A Guide to

Gulf War Veterans' Health

GULF VETS

Department of Veterans Affairs

A Guide to Gulf War Veterans' Health:

1998 Continuing Medical Education Program

Independent Study

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This Program includes:

- independent study
- test for CME credits
- program evaluation

This activity was planned and produced in accordance with the ACCME Essentials.

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Program Contents:

- History of Operations Desert Shield and Storm
- VA Healthcare Programs
- Department of Defense Comprehensive Clinical Evaluation Program for Gulf War Veterans
- Depleted Uranium
- Research on Gulf War Veterans' Illnesses
- Chemical Warfare Agents
- Some Hypotheses Regarding Illnesses in Gulf War Veterans

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1. Read the program materials.
2. Complete the registration.
3. Complete the CME test questions.
4. Complete the program evaluation.
5. A passing score of 70% on the CME test is required to receive credit. This test may be retaken one time.
6. The estimated study time for this program is six hours.

Department of Veterans Affairs
Employee Education System
St. Louis Center (14B/JB)
VA Medical Center
#1 Jefferson Barracks Drive
St. Louis, MO 63125

Purpose: This independent study is designed to provide an introduction to issues regarding Gulf War (GW) veterans' health. It will provide an overview of the Gulf War experience, the Department of Veterans Affairs (VA) and the Department of Defense (DoD) health programs available for Gulf veterans, and the common symptoms and diagnoses of these veterans. Emphasis is placed on providing the most recent available information from clinical and scientific studies of Gulf War veterans' illnesses.

Objectives: After reading this independent study, the participants will be able to:

1. recognize the most common symptoms and diagnoses of GW veterans,
2. describe current GW veterans' programs available through VA and DoD, and
3. discuss recent research studies and findings concerning health of GW veterans.

Target Audience: This independent study is designed for all VA physicians.

Planning Committee

Karen Jones, R.N., M.S.
Education & Performance Development
Division, Employee Education System
St. Louis Center
VA Medical Center, St. Louis, MO

Susan Mather, M.D., M.P.H.
Chief, Office of Public Health and
Environmental Hazards Officer
Department of Veterans Affairs
Washington, DC

Frances M. Murphy, M.D., M.P.H.
Director, Environmental Agents Service
Department of Veterans Affairs
Washington, DC

Susan K. Sverha, M.S.N.
Educational Services & Partnerships Division
Employee Education System
Department of Veterans Affairs
Washington, DC

Editor

Frances M. Murphy, M.D., M.P.H.
Director, Environmental Agents Service
Department of Veterans Affairs
Washington, DC

Program Director

Karen Jones, R.N., M.S.
Education & Performance Development
Division, Employee Education System,
St. Louis Center
VA Medical Center, St. Louis, MO

Program Assistant

Lynda Gavaghan
Site & Logistical Support Division
Employee Education System, St. Louis Center
VA Medical Center, St. Louis, MO

Learning Technology and Media Development

Jane Clanton, B.F.A., M.B.A.
Learning Technology & Media Development
Division, Employee Education System
St. Louis Center
VA Medical Center, St. Louis, MO

Deborah A. Dorsey, M.Ed.
Learning Technology & Media Development
Division, Employee Education System
St. Louis Center
VA Medical Center, St. Louis, MO

Lisa McClanahan
Learning Technology & Media Development
Division, Employee Education System
Salt Lake Center
VA Medical Center, Salt Lake City, UT

Editorial Staff

Michael Howe, M.S.L.S.
Medical Librarian
VA Medical Center, San Francisco, CA

John E. Kraemer, M.H.A.
Senior Program Analyst
Environmental Agents Service
Department of Veterans Affairs
Washington, DC

Donald J. Rosenblum
Deputy Director
Environmental Agents Service
Department of Veterans Affairs
Washington, DC

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To receive credit for this course, you must read the independent study, complete the Registration , the Test and Program Evaluation.If you have attained a passing score of at least 70%, a certificate will be mailed to you after your test has been graded (approximately 6-8 weeks).. The test may be retaken one time.

This program will no longer be authorized for CME credit after March 1999.

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Chapter One: History of Operations Desert Shield and Desert Storm

On August 2, 1990, Iraq invaded Kuwait. In accordance with United Nations Resolutions 660, the United States promptly responded by sending troops to the Gulf region to help in the defense of neighboring countries and to reverse the Iraqi aggression against Kuwait. The mission was called Desert Shield.

On August 8, 1990, the United States began deployment of almost 697,000 troops to the Southwest Asia theater of operations. The pace of military build-up was unprecedented. Furthermore, the Gulf War presented U.S. forces with many other new challenges including the deployment of large numbers of reserve and National Guard forces (approximately 17%) as well as active duty personnel, and deployment of a uniquely large number of women to combat support functions (7.2%). The demographic characteristics of the U.S. military forces are presented in Table I.

About five months later, on January 16, 1991, the air war began, and Operation Desert Shield turned into Operation Desert Storm. On February 24, 1991, the ground war began for U.S. military personnel. One hundred hours later, on February 28, 1991, the fighting ended. While Iraqi forces suffered terrible personnel casualties, the coalition forces, lead by the U.S., succeeded in liberating Kuwait and sustained far fewer combat casualties than had been anticipated. Many had expected thousands of U.S. fatalities. Well under a tenth of one percent of the U.S. 697,000 U.S. troops deployed were lost during the quick and decisive war. Furthermore, the incidence of non-battle injuries and diseases was very low in comparison with other wars or military engagements. The low morbidity was attributed to preventive medicine efforts, minimal contact with local populations, and almost no consumption of alcohol.

In contrast to the decisive victory, living conditions were far from hospitable. U.S. troops entered an extremely hot and bleak desert environment where their numbers were initially dwarfed by the large Iraqi force. A significant number of U.S. military personnel in the region spent months isolated in the desert, under constant stress, and uncertain if and when they might return home. The troops were more than 7,000 miles from the U.S. They had few amenities and lived under arduous and austere conditions. The weather, initially extremely hot, changed to cold and damp conditions by the time the Gulf War actually began.

Troops were housed in crowded warehouses, military compounds, and tents, which accorded little privacy. Prepackaged meals were sometimes their principal diet. Sanitation was far from ideal. Latrines and communal washing facilities were common. Desert filth flies were ubiquitous.

Considering the living conditions that Gulf War (GW) veterans were exposed to while in Southwest Asia, it is not surprising that some of them now have medical problems. In addition, it is important to keep in mind that GW veterans were potentially exposed to a wide range of toxic substances and environmental hazards. There has been a great deal of speculation about what may have caused the illnesses that GW veterans are currently experiencing. VA and other departments and agencies are evaluating possible causes. (See Chapter 5, which focuses on scientific research efforts.)

Most symptoms experienced by GW veterans can be easily diagnosed and effectively treated. Other symptoms have proven difficult to diagnose. These symptoms have been attributed by veterans to one or more of the following exposures: chemical or biological warfare agents, pyridostigmine bromide prophylaxis, vaccinations for botulinum toxoid and anthrax, infectious diseases, depleted uranium, oil well fires, pesticides, chemical agent-resistant coatings (CARC) paint, stress and a combination of these exposures.

One major concern that has generated considerable interest in Congress and the news media is exposure to chemical and biological warfare agents. Iraq was known to have used chemical weapons in other recent conflicts. In anticipation of their use in the Gulf War, tens of thousands of chemical agent sensors were used to detect the presence of these agents during the War. Unfortunately, chemical warfare sensors are also sensitive to numerous other substances. Consequently, there was an extraordinarily high rate of alarms.

Table I

Percent Distribution of Military Characteristics of VA Registry Participants and Gulf War Participants

Characteristics	*VA Registry (N = 52,835)*	*Gulf War (N = 696,562)*
Military Components		
Active	54.6	83.3
Reserve	20.3	10.4
National Guard	18.8	6.3
Unknown	6.4	—
Branch of Service		
Army	72.3	50.4
Marine Corps	12.2	14.9
Navy	7.7	22.7
Air Force	7.3	11.9
Coast Guard	0.3	0.1
Unknown	0.3	—
Rank		
Enlisted	88.0	89.1
Officer	12.0	10.9
Gender		
Men	89.6	92.5
Women	10.4	7.2
Race/Ethnicity		
White	65.0	67.7
Black	22.9	22.6
Other	12.1	9.7
Mean Age (years)		
(in 1991)	30.5	28.0

Source: Defense Manpower Data Center, Department of Defense

A related concern is pyridostigmine bromide, a medication used for decades in treating patients with myasthenia gravis. During the Gulf War, U.S. troops used it for the first time as an investigational new drug for pretreatment of nerve gas exposure.

Some veterans are worried that certain vaccines, specifically the immunizations for botulinum toxoid and anthrax, may have caused long-term illnesses in some veterans. Another fear is endemic infectious diseases such as leishmaniasis, Q fever, and brucellosis. Concerns about the transmission of leishmaniasis led to a temporary suspension of blood donations by GW veterans.

A unique environmental hazard of the War was exposure to depleted uranium (DU) munitions that were used for their armor penetrating ability. Some U.S. troops were exposed to DU during friendly fire incidents; others were exposed to DU while fighting a fire in a munitions storage area and/or while servicing vehicles hit by DU munitions.

Iraqi soldiers started numerous oil well fires in Kuwait at the end of the war. These fires produced dense clouds of soot, liquid aerosols, and gases. The smoke from these fires blackened the sky for days and heightened concern about respiratory problems in GW veterans.

Numerous pesticides were used in Southwest Asia. While no cases of acute pesticide poisoning are known to have occurred during these operations, the possibility that certain pesticides could have increased the acute toxic effects of pyridostigmine is being investigated.

Vehicles and equipment were painted with CARC before arriving or in the theater of operations. CARCs contain toluene diisocyanate, which could lead to pulmonary effects, including asthma. A very small number of GW veterans are thought to have had exposure to CARC while painting vehicles.

With thousands of ill GW veterans and so many potential causes, VA, in concert with other federal departments and agencies, has been proactive in developing a comprehensive program to respond to veterans' needs. The succeeding chapter describes our healthcare, surveillance and medical treatment initiatives.

Chapter Two: VA Healthcare Programs

A. VA Gulf War Veterans Health Examination Registry

Almost 697,000 active duty service members and activated reserve and National Guard from the United States served in the Gulf theater of operations during operations Desert Shield and Desert Storm. Returning U.S. troops began reporting a variety of illnesses which they initially attributed to inhalation of fumes and smoke from burning Kuwaiti oil well fires. Many other risk factors were eventually raised by veterans. Differences in military specialty determined the kinds of elements to which troops were exposed. These exposure concerns include:

- smoke from oil well fires
- smoke or fumes from tent heaters
- passive cigarette smoke from others
- diesel and/or other petrochemical fumes
- exposure to burning trash/feces
- skin exposure to diesel or other petrochemical fuel
- CARC (Chemical Agent Resistant Compound)
- other paint, solvents and petrochemical substances
- depleted uranium
- microwaves
- pesticide or personal insect repellents including creams, sprays and pet flea collars
- nerve gas or other nerve agents
- pyridostigmine bromide used to protect against nerve agents
- mustard gas or other agents
- food and drink contaminated with smoke, oil or other chemical
- potable and bathing water contaminated with smoke, oil, and/or other chemical
- endemic infections
- multiple immunizations, including against anthrax and botulism

In August 1992, in response to veterans' health concerns, VA developed a health surveillance system which evolved into the Persian Gulf Registry Health Examination Program.

Persian Gulf Registry

The Persian Gulf Registry Health Examination Program offers a free, complete physical examination with basic laboratory studies to every GW veteran. A complete medical history is also performed and documented in the veteran's medical record. To date, almost 67,000 veterans have responded to VA's outreach program encouraging them to obtain a free physical examination. A centralized registry (list of participants who have had these examinations) is maintained to enable VA to keep veterans informed on research findings or new compensation policies through periodic newsletters. This clinical database is called the Persian Gulf Veterans Health Registry, which in addition to allowing VA to communicate with GW veterans, provides a mechanism to catalogue prominent symptoms, reported exposures, and diagnoses. The voluntary, self-selected nature of the database make it valuable for health surveillance; however, it is not designed or intended to be a research tool and therefore, the results cannot be generalized to represent all GW veterans' illnesses. Each VA medical center has an assigned Registry Coordinator and a Registry Physician.

Protocol

The standard Registry examination protocol (Protocol for Conducting the Physical Examination and Ordering Diagnostic Studies) consists of the laboratory tests and consultations that physicians use to evaluate the symptoms reported by GW veterans during their initial physical examination. This basic examination protocol extracts information about symptoms and exposures, and directs baseline laboratory studies, including blood count, urinalysis and a set of blood chemistry tests. VA has expanded this standard protocol as more experience has been gained about the health of GW veterans. In addition to this core laboratory work, for every veteran taking the Registry examination,

physicians order additional tests and specialty consultations as symptoms dictate. If a veteran's symptoms remain unexplained, VA provides an expanded assessment protocol, which is in essence a set of clinical guidelines for use in evaluating ill-defined or unexplained illnesses of GW veterans. An unexplained illness for this purpose is one or more symptoms that do not conform to the characteristic set of signs or symptoms allowing a conventional diagnosis to be made, but are causing a decline in the veteran's functional status or quality of life.

This set of clinical guidelines, the Uniform Case Assessment Protocol (UCAP), suggests 22 additional baseline tests and auxiliary specialty consultations and outlines supplementary diagnostic procedures based on the specific symptoms of the veterans and the clinical judgment of the Veterans' Registry Physician. The UCAP was originally developed in 1993 for use by the VA's Referral Centers (described in Section B), but is now standardized and used in VA and Department of Defense (DoD) medical centers nationwide. In January 1996, the Institute of Medicine (IOM) completed a two-year study of DoD's Persian Gulf Comprehensive Clinical Evaluation Program (CCEP). The CCEP was developed to respond to the health problems experienced by active duty military personnel following their service in the Persian Gulf. It provides an in-depth systematic medical evaluation for DoD personnel utilizing the UCAP. The IOM's final report included the following recommendations and comments regarding the CCEP/UCAP:

- The CCEP clinical protocol is a thorough, systematic approach to the diagnosis of a wide spectrum of diseases.
- The results of the CCEP can and should be used for several purposes, including education, improving the medical protocol itself, and evaluating patient outcomes.

The required forms that must be completed as part of the Persian Gulf Registry Health Examination Program are: Standard Form (SF) 88, Report of Medical Examination, VA Form 10-9009A, Persian Gulf Registry Code Sheet, and SF 509, Progress Notes (for follow-up). These are maintained in the veteran's Consolidated Health Record (CHR). Completion of the forms should be accomplished by, or under the direct supervision of, a Veterans' Registry Physician.

In VA and DoD registries, no significant variation in occurrence of major categories of medical problems has been identified, but there has been a wide distribution of major categories of diagnosis. The International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM), does not provide sufficient codes to correctly identify all symptoms and diagnoses. Several new coding designations have been created to correct this problem. Form 10-9009A lists a number of diseases and exposures endemic to the Gulf area to help familiarize examining physicians with some of the health problems and/or diseases they should consider when rendering diagnoses.

Enrollment

While GW veterans cannot gain inclusion to the Persian Gulf Health Examination Registry merely by requesting to be added to the list, the individuals who have taken advantage of the physical examination program become part of a larger Persian Gulf consolidated "Registry" or roster of GW veterans. Eligibility under Public Law 102-585 (Title VII), the "Persian Gulf War Veterans Health Status Act" (enacted November 4, 1992), allows for GW participants to be included in the consolidated roster if they meet one of the following criteria:

1. apply for health services from VA,
2. file a claim for compensation from VA on the basis of any which may be associated with GW service,
3. die and are survived by a spouse, child or parent who files a VA claim for dependency and indemnity compensation (survivors' benefits) on the basis of GW service,
4. request a special VA Registry health examination (authorized by this law), or

5. receive a health examination from the Department of Defense similar to the VA Registry examination, and request inclusion in the VA Registry.

Currently, more than 200,000 veterans are included on the consolidated roster. VA uses this roster for outreach to GW veterans.

Results

Not all of the almost 67,000 GW veterans who have received a free Registry physical examination are ill. The self-reported health status of 52,835 of these individuals shows that 32.2% report their health was very good/good, 40.8% report their health was good, and 25.6% report their health was poor/very poor. The 10 most frequent complaints of these 52,835 Registry veterans, and the distribution of diagnoses are shown in Tables I and II.

Table I
Ten Most Frequent Complaints Among the 52,835 Veterans on the Persian Gulf Registry

Complaints	*Frequency*	*Percent**
Fatigue	10,847	20.5
Skin Rash	9,719	18.4
Headache	9,525	18.0
Muscle, Joint Pain	8,871	16.8
Loss of Memory and Other General Symptoms	7,406	14.0
Shortness of Breath	4,190	7.9
Sleep Disturbances	3,111	5.9
Diarrhea and Other GI Symptoms	2,416	4.6
Other Symptoms (Involving Skin and Integumentary Tissue)	1,916	3.6
Chest Pain	1,847	3.5
No Complaint	6,496	12.3

*Percent of 52,835 veterans

(Data as of August 1997, prepared by Office of Public Health and Environmental Hazards)

Table II
Distribution of Diagnoses for the 52,835 Veterans on the Persian Gulf Registry

Diagnosis	*Number*	*Percent*
Infectious Diseases	3,715	7.0
Neoplasm	232	0.4
Mental Disorders	7,995	15.1
Nervous System	4,398	8.3
Circulatory System	3,747	7.1
Respiratory System	7,540	14.3
Digestive System	6,028	11.4
Genitourinary System	1,774	3.4
Skin & Subcutaneous Tissue	7,144	13.5
Musculoskeletal and Connective Tissue	13,299	25.2
Injury and Poisoning	2,485	4.7
No Medical Diagnosis	13,998	26.5

(Data as of August 1997, prepared by Office of Public Health and Environmental Hazards)

Limitations

The VA's Persian Gulf Registry Health Examination Program is a clinical care program offering a voluntary health examination to every GW veteran concerned about their health status. The computerized clinical database developed from these examination results provides valuable information about types of symptoms and illnesses experienced by GW participants. However, since the Registry database consists of a self-selected population, lacks an appropriate comparison or control group, and is subject to recall bias, it cannot be used to identify the etiology of a disease or estimate prevalence. The Persian Gulf Registry Health Examination Program is not a research tool, but the information it generates may eventually suggest areas to be explored in directed scientific epidemiologic research studies.

B. Referral Centers

For GW veterans with severe symptoms that remain unexplained after taking a Registry health examination, the local VA physician may refer them to one of VA's four Persian Gulf Referral Centers. VA determined that for these veterans, it is desirable to provide hospital stays to allow for observation, multidisciplinary consultation, documentation of occupational and exposure histories, and opportunity for frequent re-examination.

Locations

Created in 1992, the first centers were located at VA medical centers in Washington, D.C., Houston and Los Angeles. In June 1995, an additional Persian Gulf Referral Center was designated at Birmingham, AL. The referral centers were selected on the basis of clinical and academic

expertise in such areas as neuropsychology, immunology, toxicology, and pulmonary and infectious diseases.

Referral

The majority of the veterans who have reported to their local VA medical center for a health examination have been successfully diagnosed there. The decision to send a veteran to a referral center is made by the local medical center physician in consultation with a referral center physician. The number of veterans requiring transfer to a referral center has been relatively small. More than 400 have been assessed at the referral centers thus far. Most of these individuals have been ultimately diagnosed with known or definable illness. Individuals who feel they may benefit from a referral center evaluation should contact their local VA physician.

Unexplained Illnesses

The prevalence of unexplained illnesses among GW veterans is uncertain. Although most GW veterans are diagnosed and treated, some experience such chronic symptoms as fatigue, memory loss, or joint pain. Some respond to well-accepted symptomatic treatments even though their doctors have not identified a pathogenic agent or underlying illness. There appears to be no unifying exposure that would account for all unexplained illnesses. Several panels of private-sector medical and scientific experts and government physicians have been unable to identify any unique symptom complex or new illness such as that incorrectly referred to as "Persian Gulf Syndrome."

C. VA-Funded Examination Program for the Spouses and Children of GW Veterans

On April 1, 1996, VA initiated a special program to fund health examination for some spouses and children of GW Veterans Registry participants. The results of these examinations, which are conducted under contract by non-VA physicians in non-VA medical facilities, are included in the Registry. This program was established by Public Law 103-446 which originally authorized funding for six months. The legislation has recently been amended to extend funding through December 31, 1998.

Eligibility

Under this authority, VA can provide examinations to any individual, who:

a. is the spouse or child of a veteran, is listed in the Persian Gulf War Veterans Registry established under P.L. 102-585, Section 702; and is suffering from illness or disorder.

b. is suffering from, or may have suffered from, an illness or disorder (including birth defect, miscarriage, or stillbirth) which cannot be disassociated from the veteran's service in the Southwest Asia theater of operations.

c. has granted VA permission to include in the Registry relevant medical data from the evaluation.

Administration

Individuals wishing to participate can register for the program by calling the VA Persian Gulf War Helpline (1-800-PGW-VETS). Helpline personnel enter the required information into a computer database which is forwarded to VA Headquarter's Environmental Agents Service. Information on participants whose eligibility is confirmed is then forwarded to the appropriate Veterans Integrated Service Network (VISN) office. Each Network Director designated at least one tertiary care center in his/her VISN to participate. The 35 designated VAMCs establish a contract with their affiliated university to perform the protocol examinations. Examinations are performed by a board-certified/eligible physician. Payment for the examinations performed under this program are authorized only after the contract physician submits all forms and completed code sheets to the responsible VAMC.

Protocols

The protocol for examination of GW veterans' spouses involves a signed informed consent form, VA Form 10-21002a, Consent to Participate in VA's Registry Examination Program for Spouses and Children of Persian Gulf Veterans, VA Form 10-9009c, Persian Gulf Registry Code Sheet (Spouse or Child of Persian Gulf Veteran), and VA Form 10-21002d, Adult Symptom Checklist. A physical examination is completed and recorded on the adult standardized exam form, VA Form 10-21002b, Funded GW Spouses and Children Examination Program. Diagnostic testing includes a complete blood count, blood chemistries (chem 20), urinalysis, and, for women, a Pap smear, and breast and pelvic examination. Upon completion of the evaluation, VA Form 10-9009c is completed and signed by the examining physician.

The protocol for children of GW veterans includes a detailed medical history including symptoms and developmental history. A physical examination is completed and recorded on the juvenile standardized examination form, VA Form 10-21002c, Funded GW Spouses and Children Examination Program. No routine diagnostic testing is required by the protocol.

Alternative Program

Eligible family members of GW veterans may have their medical information entered into the Persian Gulf Registry database by undergoing a physical examination from their private physician. The physician must complete a Registry code sheet containing the protocol examination information and submit it to VA for entry into the database. The veteran or family member choosing this option must assume the cost of the protocol examination and code sheet completion.

Informed Consent

Requiring participants to sign an informed consent form (VA Form 10-21002a) not only permits VA to enter their health information into the Registry database, it also serves to inform them that no follow-up examinations or treatment are provided.

D. Priority Care Eligibility for Gulf War Veterans

Currently, GW veterans are granted, by legislative mandate, special eligibility status for VA healthcare. If a condition is found, which the VA examining physician determines could possibly be related to an exposure which occurred during service in the Gulf War, that condition will be treated and medical care provided at no cost to the veteran. If the physician determines that the condition could not in any way be associated with an exposure during GW service, the physician enters this medical opinion in the veteran's consolidated health record. A traumatic injury sustained years after service is an example of such a condition.

Chapter Three: Department of Defense Comprehensive Clinical Evaluation for Gulf War Veterans

Introduction

In 1994, in response to GW veterans' concerns about possible health effects of service in Operations Desert Shield and Desert Storm, the Department of Defense (DoD) developed a special clinical examination program, the Comprehensive Clinical Evaluation Program or CCEP. Individuals eligible for the CCEP include GW veterans currently on active duty or retired, members of the full-time National Guard who are GW veterans, and GW veterans who are members of the Ready Reserve/Individual Ready Reserve/Standby Reserve or Reserve components and their family members. This examination program was modeled after the Department of Veterans Affairs Persian Gulf Registry Health Examination and provides comparable clinical guidelines and evaluations. Both DoD's CCEP and VA's Registry were designed primarily as a clinical rather than a research program. Self-selection of patients, inability to validate self-reported exposures, and lack of an appropriate control group limit our ability to draw generalizable conclusions from these examination programs. However, the large numbers of individuals examined and the systematic examination process provide important clinical insight into the variety of illnesses suffered by GW veterans and a source of hypotheses for future research.

Reference: ***A Comprehensive Clinical Evaluation of 20,000 Gulf War Veterans***
Military Medicine. 1997 Mar;162(3):149-155.

Authors: Stephen C. Joseph, M.D., M.P.H. and the Comprehensive Clinical Evaluation Program Evaluation Team

Background

During the six years since the end of the Gulf War on February 28, 1991, some veterans of Operations Desert Shield and Desert Storm have presented with a diversity of unexplained somatic symptoms. Although various potential etiologies have been postulated, no single cause of these symptoms has been demonstrated. In response to the health concerns of GW veterans, DoD instituted the CCEP on June 7, 1994. Although not designed as a research study, the CCEP nevertheless provided valuable clinical information about the health of this population. This report is an analysis of the findings from the comprehensive clinical evaluation of 20,000 GW veterans.

Methods

Starting on August 8, 1990, the U.S. deployed 697,000 troops to the Gulf region; by May 1991, most had returned. Troops who remained on active duty after the war were provided complete healthcare. In addition, the physical condition of active duty U.S. troops is assessed continuously with physical fitness tests every six to 12 months, routine dental and gynecological examinations, and a complete medical examination at least every five years. Prior to leaving active duty, military personnel are medically screened and undergo a physical examination.

The 285,000 GW veterans still on active duty when the CCEP was initiated were encouraged to participate if they had any health questions or concerns. The CCEP provided a two-phase clinical evaluation supervised by a board-certified physician. All participants were provided a Phase I examination. For those without current medical problems or who had health problems that could be satisfactorily explained, no additional evaluation was conducted. If referral consultations and specialized tests were clinically indicated, participants proceeded to Phase II examination at one of 14 DoD regional medical centers. At the conclusion of the CCEP evaluation process, examining physicians provided a primary diagnosis and additional secondary diagnoses based on clinical importance. After review by accredited medical record coders, up to seven diagnoses were coded using the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM) and entered into the data base.

Results

As of April 1, 1996, a total of 20,000 GW veterans had completed CCEP examinations with 12% of participants undergoing specialized Phase II evaluations. The types of primary and secondary diagnoses among CCEP participants varied widely. For broad ICD-9-CM classifications, the three most common primary diagnoses were "diseases of the musculoskeletal system and connective tissue" (18.6%), "mental disorders" (18.3%), and "symptoms, signs, and ill-defined conditions" (17.8%). Nine percent of participants were found to be "healthy" without a clinically significant new illness.

Among the 3,558 participants with a primary diagnosis of "symptoms, signs, and ill-defined conditions," no single ICD-9-CM subcategory predominated. These veterans had a wide variety of symptoms, with fatigue, headache, memory problems, and sleep disturbances being the most frequent presenting complaints.

Among all 20,000 CCEP participants, the examinations revealed the following diagnoses: connective tissue disease as either a primary or secondary diagnosis (74 participants); disorders of immunity (5 with selective immunoglobulin A immunodeficiency and 1 with selective immunoglobulin M immunodeficiency); skin cancer (9), lymphoma/leukemia (22), other types of cancers (30); glomerulonephritis (13) and renal insufficiency (12); interstitial pulmonary fibrosis (14); and polyneuropathy (8) or peripheral neuropathy (34). Common skin infections accounted for 60% of primary infectious disease diagnoses. A common or distinctive organic pathology was not identified among over 800 veterans with neuromuscular symptoms who had extensive neuropsychological evaluations.

All elicited exposures were reported frequently, including: exposure to diesel and other fuels (88%); use of pyridostigmine bromide pills (74%); exposure to oil well fire smoke (71%); personal use of insect repellents (66%); anthrax (49%) and botulinum (26%) vaccinations; and observing combat casualties (57%) or actual combat (38%).

Discussion

This large patient series demonstrated a wide range of well-known illnesses among GW veterans requesting evaluation, with no single illness predominating and no clinical indication of a new or unique syndrome. In addition, the types of medical conditions that would result from postulated Gulf War environmental hazards were diagnosed infrequently, including: neurologic disease from possible chemical weapons or pesticide exposure, interstitial pulmonary disease from smoke or sand inhalation, renal disease from heavy metal exposure, and immunologic dysfunction from various combinations of exposures. These findings are consistent with medical surveillance data collected during the Gulf deployment. Also, the absence of clinical data indicating a new or unique illness is consistent with the findings of three previous review panels that did not identify a distinctive syndrome related to GW service.

A relatively large percentage of CCEP participants had a psychological condition as either a primary (18%) or secondary (18%) diagnosis. Also a large number of troops had musculoskeletal conditions. The third common diagnostic category, "symptoms, signs, and ill-defined conditions," did not appear to represent a group of veterans with a distinctive illness. CCEP participants in this diagnostic category varied substantially in clinical presentation; no characteristic physical sign or laboratory abnormality was identified.

These clinical findings have to be carefully qualified by the fact that the CCEP was not designed as a research study. In addition, a rare or minimally pathogenic illness could have been missed or not adequately captured in the data base because of diagnostic weakness of the ICD-9-CM coding system. Nevertheless, any widespread serious physiologic disease should have been detected in this very large patient series. It also is unlikely that debilitating disease would remain undetected among active duty troops not participating in the CCEP because of the military's emphasis on readiness and preventive medicine, including regular physical evaluations of troops. Because the CCEP primarily involved active duty troops, any illness that predominated among Reserve/National Guard personnel or veterans who had been discharged from the military would have been under-represented in the CCEP population. However, no new or unique illness has been identified.

Although a new or unique illness was not identified, the findings of the CCEP nevertheless provide important clinical information. In the evaluation of GW veterans, physicians will need to be alert for a wide range of illnesses because the diversity of medical and psychological problems that occur in any sizable adult population was found in this cohort. In addition, the findings of the CCEP provide reassurance for GW veterans

since effective treatments are available for most commonly diagnosed health problems. Inability in this and prior clinical evaluations to find a characteristic organic sign of a new or unique disease among GW veterans will result in research limitations not encountered in studies of well-characterized diseases. Most importantly, a specific case-definition based on criteria that can be objectively measured cannot be developed without a characteristic sign of pathology. Any definition of illness will have to be based on self-reported symptoms which are subject to confounding and recall bias in a population that has been the focus of widespread publicity about possible harmful exposures and ill health.

Veterans' health questions remain unresolved because the causes, frequency, and long-term sequelae of nonspecific somatic symptoms are not adequately understood. Until they are better understood, it will be difficult to thoroughly determine the health of any large adult population, whether military or civilian.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

Chapter Four: Depleted Uranium

Introduction

Depleted Uranium (DU) is the component of natural uranium ore left after the U235 is removed for use as fuel in nuclear power reactors. Consequently, DU has approximately half the radioactivity of naturally occurring mineral deposits of uranium. DU also has nephrotoxicity and neurotoxicity related to its heavy metal properties.

In recent years, the United States Armed Forces have used DU in manufacture of projectiles and armor for vehicles. It is used in anti-tank munitions because of its highly effective penetrating capabilities and as protective armor plating due to its extremely dense properties.

During the Gulf War, some U.S. tanks and airplanes fired DU munitions which produced shrapnel and an aerosolized dust upon impact with armor. A friendly fire incident injured approximately three dozen U.S troops in a Bradley fighting vehicle. Other GW veterans had potential exposure to DU during reclamation, decontamination and restoration of damaged vehicles.

In 1993, VA established a special medical surveillance program at the Baltimore VA medical center to follow those GW veterans identified by the U.S. Army to have retained DU shrapnel. The program provides periodic evaluations to monitor for potential adverse health consequences of retained depleted uranium fragments.

Depleted Uranium: General Information

What is Depleted Uranium?

Depleted uranium is derived from the heavy metal uranium, which occurs naturally as mineral deposits which are mined and processed primarily for use as fuel in nuclear power reactors. Naturally occurring uranium (U nat) deposits contain over 99% U238, with small amounts of U235 and U234. U238 has a half life of 4.5 billion years but has very low radioactivity. Depleted uranium is the natural uranium left over from the concentration and extraction of U235. It contains even less U235 than naturally occurring ores. The spent uranium which is about half as radioactive as natural uranium is the "depleted uranium." (Voelz)

How does the military use Depleted Uranium?

In recent years, the United States Armed Forces have used depleted uranium (DU) in the manufacture of both projectiles and armor. Uranium's high density and pyrophoric or easily combustible properties makes it, in projectiles, capable of penetrating armor made with less dense metals. Conversely, armor constructed with DU provides a high degree of shielding and resistance to penetration. During the Gulf War, depleted uranium containing munitions were used on a very large scale for the first time. In the manufacture of projectiles and armor, depleted uranium is alloyed with small amounts of other metals such as molybdenum, titanium, zirconium and niobium. (DoD, 1993)

How were soldiers exposed to DU?

When a vehicle is impacted and penetrated by a DU projectile, the projectile splits into small shards, bursts into flames, and fills the insides of the vehicle with flying metal, fumes, and particulates. The inside of the damaged vehicle remains contaminated. In the event of a vehicular fire, the heat of the fire can cause any onboard DU ammunition to oxidize. Soldiers in struck vehicles may inhale airborne DU particles (or other combustion products), ingest DU particles, and experience wound contamination by DU. Crew members may be left with multiple tiny fragments of uranium scattered through their muscle and soft tissue. Other soldiers may exposed during operations to salvage tanks that had been disabled by DU rounds or have potential exposure from brief "sightseeing" entry into damaged vehicles.

Who was exposed to DU in the Gulf War?

At present only a limited number of U.S. veterans are known to have been directly wounded by DU weapons. An initial check by the Army's Office of the Surgeon General (OTSG) has revealed that there are approximately 22 soldiers whose records indicated shrapnel fragments that might contain DU. There are an additional 13 soldiers with potential DU exposure who were wounded and hospitalized but were not specifically identified as having shrapnel.

It is possible that some other allied personnel were wounded by DU munitions. US forces continue to use DU munitions and may employ them in future conflicts. DU penetrators are now available in international arms markets, and may become widely available to armies around the globe. Other groups with potential exposure to DU include personnel involved in the assessment, reclamation, decontamination and restoration of damaged vehicles as well as workers involved in the maintenance or modification of armored vehicles.

Are there civilian groups exposed to DU?

Workers involved in the manufacture and testing of DU munitions and fabrication of armor, as well as those involved in the assembly of vehicles, may also form a potentially exposed population. Environmental contamination of soil, water, air

and food may pose a risk to the general population from DU penetrators, fragments or dust scattered on battlefields and training grounds. The potential for stateside environmental contamination of soil, water, air and food remains as well. In 1991, according to the Wall Street Journal, an estimated 705 million pounds of DU were stockpiled in the U.S. Consideration of other uses of DU, including use as a replacement for lead in bird shot, yacht keels and ballast, and aircraft and missile counterweights, suggest the possibility of future exposed populations.

References:

Voelz, George L., Chapter 13 Uranium in Hazardous Material Toxicology Eds. Sullivan, John B. and Krieger, Gary R.Williams and Wilkins, Baltimore, MD 1992.

Health Effects of Depleted Uranium - Fact Sheet, Department of Defense, June 11, 1993. Copies can be obtained by calling 703-697-3189.

Depleted Uranium: Health Effects

How does DU enter the body?

The uptake and distribution of uranium is in some ways analogous to other heavy metals, such as lead, mercury, arsenic, and cadmium and can enter the body through any of the three common routes of absorption. The principal entry route is through inhalation of DU vapor and fine dust contamination with DU. Dermal exposure as a result of DU dust contamination of skin or a wound is also possible. Imbedded, retained DU shrapnel may be dissolved and also be absorbed and distributed throughout the body. Depleted uranium dust can be ingested as well, but is not a likely significant exposure route unless exposure is ongoing.

What are the health effects of Depleted Uranium Exposure?

Research on the human health effects of DU exposure in military occupations is limited, especially regarding DU's potential chemical (rather than radiologic) toxicity. There are, for example, no published epidemiological studies of soldiers exposed to depleted uranium dust or vapor in war time settings. Most of the knowledge about human effects is derived from studies of uranium miners and associated occupations which is not precisely, but generally relevant to DU exposed veterans. For example, uranium miners and millers have exposure to uranium but also possibly to radon, as well as other toxic substances present in the mines or the ores that are milled, making their health effects experience not directly comparable to those DU exposed. Additionally, exposure intensity and duration of these other occupations are not directly comparable to exposure scenarios in military settings, limiting the applicability of observed health effects in the DU exposure setting.

Acute toxic effects of uranium exposure are manifested primarily in the respiratory system and kidney. In wartime situations, there is the possibility of acute exposure to DU when DU munitions or shielding explode and burn. It is theorized that soldiers, particularly soldiers inside of tanks, may inhale excessive amounts of DU vapor and dusts raising the question about local effects in the lung as well as systemic effects incurred through an inhalation exposure.

Chronic exposure is thought to affect primarily the kidney. The few chronic studies in the literature (as summarized by Voelz) document renal tubular changes without clear clinical implications. Other epidemiological studies of uranium millers and miners shows an increased risk of renal disease. Animal studies have documented both tubular and glomerular lesions in rats given uranium compounds orally. These lesions increased with higher doses of uranium. (From ATSDR Tox Profile p 43). This finding is consistent with the known health effects of other heavy metals. It is unknown if low level, chronic exposure to DU will cause renal disease.

Chronic exposure by inhalation presents a potential radiologic hazard to the lung. Uranium miners have a long occupational history of inhaling uranium dust in closed spaces. There is an increased risk of lung cancer among uranium miners but this is thought to be due to the simultaneous exposure to radon. The animal data are insufficient to determine whether inhalation of natural uranium causes lung cancer in animals.

Concerns about genotoxicity, mutagenicity and reproductive effects are only beginning to be studied, and definitive answers to these questions will almost certainly take much more work. Animal cell lines treated with uranium in one study have shown possible genotoxic and/or mutagenic changes. Reproductive effects in humans exposed to uranium have not been studied.

The ATSDR Toxicological Profile on Uranium summarizes the existing animal and human data on uranium. (See ordering information in the Section on Further Reading)

Is Depleted Uranium radioactive?

External exposures, that is when DU is not taken directly into the body, result in minimal radiation exposure because DU has low levels of radioactivity. The Department of Defense has developed estimates of radiation exposure as follows:

> Bare DU penetrator dose at distance of one meter = 0.7 mrem/hour of exposure
>
> Soldier would have to stand near bare penetrator for 700 hours to exceed allowed radiation levels for the general public. (500 mrem/year)
>
> Holding a bare penetrator for 93 hours would exceed quarterly radiation level limit allowed for occupational exposures.
>
> A soldier in a fully uploaded tank with DU munitions (0.5mrem/hour) is within allowed standards of radiation exposure for the general public.(DoD, 1993)

Internal exposure, whether via inhalation, ingestion, wound contamination or retained shrapnel warrants concern. Internalized DU radioactive particles "…are unable to penetrate skin, but can travel short distance in the body and cause damage…"[ATSDR Toxicological Profile, 1990]. Concerns about cell damage from exposure to the radioactivity of depleted uranium should be tempered with the knowledge that DU is minimally radioactive and is even less radioactive than naturally occurring uranium which is found in the soil. Nonetheless, an assessment of exposure, whether the exposure is internal, and a commitment to regular follow-up are prudent clinical and public health activities.

Are there other toxic effects of Depleted Uranium?

The original concern about health effects from DU exposure was primarily the potential radiologic hazard that exists. Separate from its radiologic properties however, uranium is also a heavy metal, a chemical toxicant which exhibits some adverse health effects similar to other heavy metals, such as lead and cadmium. The kidney effects, for example (proximal tubular and, possibly, glomerular) are likely a result of the chemical toxicity of uranium, rather than its radiologic toxicity. The mutagenicity data, although extremely limited, are also probably due to uraniumís chemical properties. This distinction is important because it suggests possible health outcomes in an affected population, as well as a knowledge base (which exists for other heavy metals) with which to compare the extremely limited findings observed in the DU exposed participants.

Insights into successful interventions, treatment strategies and refined prognoses may also be gained from the heavy metal literature. The chemical nature of DU will thus be an additional focus for the on-going follow-up program.

References:

> Agency for Toxic Substances and Disease Registry., U.S. Public Health Service. 1990. Toxicologic Profile for Uranium. PB91-180 471, US. Department of Commerce, National Technical Information Service. Customer Service (703) 487-4660.
>
> Health Effects of Depleted Uranium - Fact Sheet, Department of Defense, June 11, 1993. Copies can be obtained by calling (703) 697-3189.
>
> Voelz, George L., Chapter 13 Uranium in Hazardous Material Toxicology Eds. Sullivan, John B. and Krieger, Gary R.Williams and Wilkins, Baltimore, MD 1992.

Depleted Uranium: VA Follow-up Program

What is the Depleted Uranium Follow-up Program?

The VA Depleted Uranium (DU) Follow-up Program at the Baltimore VA Medical Center is a clinical surveillance program for identifying, characterizing and following individuals with retained DU fragments.

The specific aims of the project are to provide on-going clinical surveillance of GW veterans with known or suspected imbedded DU fragments, DU contaminated wounds or significant amounts of inhaled DU. This clinical surveillance will detect health effects, if any, of DU containing shrapnel, and provide recommendations for treatment to participating veterans and physicians caring for them.

Focused research into the toxicological and radiological effects of DU is intended to improve the scientific basis for advice about fragment removal, to better model uranium absorption, distribution in tissue, and excretion, and to develop improved methods to assess uranium dose in vivo. In addition, the program hopes to improve methods of detection of toxic effects from low dose uranium exposure.

Who is participating in the DU Follow-up Program?

Thirty-three participants, who had been on or in U.S. Army vehicles when struck by DU containing munitions, were evaluated at the Baltimore VA Medical Center in 1993 and 1994 and continue to be followed by the Program. Approximately half of the participants remain on active duty.

What is the Program doing for the participants?

All participants were evaluated at the Baltimore VA Medical Center and underwent a comprehensive medical and psychological evaluation, as well as a full body radiologic shrapnel survey. While those individuals with evidence of retained shrapnel showed increased excretion of uranium, no association between uranium excretion and clinically detectable adverse effects has been documented. Efforts to improve both the assessment of uranium dose and the detection of toxic effects continue. The Program has facilitated the assignment of primary care providers for the veterans in the group and interfaces with those primary care providers as needed.

Consultation: A toll-free telephone number has been made available to participants, as well as their family members and healthcare providers, for consultation and assistance in a variety of clinical and personal issues. The staff have expertise and experience in the area of environmental and occupational health, particularly with regard to the effects of heavy metal exposure.

Does the DU Program work with other groups involved in DU research?

The DU program has developed a collaboration of VA and non-VA academic experts in the field of exposure characterization and outcome measurement. A team of specialists in environmental and occupational health, epidemiology, toxicology, radiobiology, physics, psychiatry, neuropsychology, and reproductive health have worked individually and collectively to develop and adapt diagnostic tools to better evaluate, treat and counsel this unique group of soldiers and veterans.

What kinds of outreach and assistance efforts have been provided to non-participants and the community at large?

Consultation: The program has been involved in outreach activities to other VA medical centers, serving as a clearinghouse for questions raised by veterans about uranium exposures. These inquiries involve veterans who were not wounded but may have inhaled or been in proximity to uranium because of their active duty participation during the Gulf War or during maintenance, clean up and repair of vehicles containing depleted uranium.

While at much lower risk than program participants, these individuals still have questions for their VA physicians. The Program aids their physicians with advice about the best methods to assess the risks of past depleted uranium exposure and how to assess these exposures clinically.

Communication: The staff of the DU Program serve as a resource for requests for information from healthcare providers, government and private sector news publications, VA Headquarters, the Presidential Advisory Committee on Persian Gulf War Veterans' Illnesses, and others.

Depleted Uranium: Consultation Information

What can I do if a patient suspects possible past DU exposure as a result of military service in the Gulf War?

The staff of the DU Program has a unique expertise in the evaluation of risk, clinical assessment and treatment of exposure to depleted uranium. Based on their experience with DU and other heavy metal exposures, they are available to provide:

- general information regarding depleted uranium
- determination of possible exposure
- assessment of risk
- guidance in determining appropriate medical testing
- assistance in obtaining and interpreting urine uranium results
- advice for counseling DU-exposed personnel
- referral to other specialists for individualized problem solving

Points of contact for DU Program

To contact the DU Follow up Program:

Call 1-800-815-7533

or write

Depleted Uranium Program (11DUP)
Baltimore Veterans Affairs Medical Center
10 N. Greene Street
Baltimore, MD 21201

Depleted Uranium: Guidelines for Clinicians

Tips for Taking the History

Listen for the patients' concerns about their Gulf War exposures and experiences. Veterans are hearing information and advice from a wide variety of sources. Encourage the patient to ask questions and express their concerns. Given the amount of public discussion of possible sequelae, it is not surprising that veterans will wonder about the possible significance and prognosis of any type of new symptom in themselves or their family members. In the first round of evaluations, we uncovered serious concerns about the possible significance of problems as common and generally benign as otitis media in toddlers and tinea versicolor. Such concerns and apprehensions won't be relieved if they do not get discussed.

Ask the patient to provide a detailed description of all occupations, including the current occupation. Focus on the situation that resulted in potential DU exposure. Probe for specific details about duties, the equipment used, the nature of the site, the protective equipment worn, the training required and the hazard information provided. Obtain information about how and why the veteran believes he or she was exposed to DU. Patients can often provide quite accurate and detailed exposure information.

It is always important to determine the length of time the patient may have been exposed. For example, how many hours did the soldier spend cleaning tanks potentially contaminated with DU dust. Determine if the exposure occurred via inhalation, ingestion or dermal (wound contamination). The clinician can reassure most concerned patients by pointing out that in the cohort with imbedded, retained DU shrapnel, no adverse health conditions have been detected. The clinician should emphasize that retained shrapnel represents continuous, internal exposure and, as such, is more potentially hazardous than other military exposures as currently understood. The clinician can further re-assure the patient by assessing uranium excretion when indicated by the individual's exposure history. (See next section.)

Laboratory Tests for Uranium

The only practical, biologic measure readily available to assess uranium exposure clinically is to measure urine excretion of uranium. If internal DU exposure is suspected, the clinician should call the DU Program to discuss the specific patient case. The DU Program at the Baltimore VAMC will facilitate processing and interpretation of the results. The results are available in four to six weeks and the clinician will be called with the results and interpretation. Other possible methods for assessing DU exposure and body burden are being developed and are not appropriate for routine, clinical use.

Depleted Uranium: Further Reading

Uranium and Depleted Uranium

Agency for Toxic Substances and Disease Registry., U.S. Public Health Service. 1990. *Toxicologic Profile for Uranium*. PB91-180 471, US. Department of Commerce, National Technical Information Service. Customer Service 703-487-4660.

Armed Forces Radiobiology Research Institute. *Technical Report 93-3, Depleted Uranium: Questions and Answers*. Prepared by: CDR Eric E. Kearsely, MSC, USN and LTC Eric G. Daxon, MS, USA

Health and Environmental Consequences of Depleted Uranium Use by the U.S. Army, Summary Report to Congress, Prepared by U.S. Army Environmental Policy Institute, June 1994.

Health Effects of Depleted Uranium - Fact Sheet, Department of Defense, June 11, 1993. Copies can be obtained by calling 703-697-3189.

Voelz, George L., Chapter 13 *Uranium in Hazardous Material Toxicology*. Eds. Sullivan, John B. and Krieger, Gary R.Williams and Wilkins, Baltimore, MD 1992.

Gulf War Illness

Institute of Medicine, Committee to Review the Health Consequences of Service During the Persian Gulf War. *Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Immediate Action* (Washington, DC: National Academy Press, 1995)

Presidential Advisory Committee on Gulf War Veterans Illnesses: Interim Report. Washington, DC: U.S. Government Printing Office, February 1996)

On the Internet

GulfLINK (http://www.dtic.dla.mil/gulflink/) is the World Wide Web information system of the Persian Gulf War Veterans Illnesses Task Force which provides to the public information concerning the illnesses affecting Gulf War veterans. Information is updated periodically and covers a wide range of topics. For example, recent searches produced access to information such as Federal Activities Related to the Health of Persian Gulf Veterans: Dept. of Veterans Affairs, March 1995 which details VA and DoD research on depleted uranium, as well as testimony from the Presidential Advisory Committee on Gulf War Veterans' Illnesses on August 6, 1996.

Chapter Five: Research on Gulf War Veterans' Illnesses

Introduction

On August 31, 1993, in response to Public Law 102-585, President William J. Clinton asked the Secretary of Veterans Affairs to take the lead in coordinating research into the health consequences of GW service. VA is committed to investigating all possible causes and treatments for health problems in troops who served in the Gulf War. The President has declared that federal researchers should "leave no stone unturned" in the search for answers to the questions raised by GW veterans and their families about the long-term health effects of military service in the Gulf War.

The Departments of Defense and Health and Human Services also are pursuing important research efforts. More than 90 federally-funded projects are in progress, and others have been completed. Nearly half of all GW research is being conducted at VA hospitals and affiliated medical schools. Important VA research projects include a long-term mortality study of GW veterans, and a national health survey of GW veterans and their families. In 1994, VA established three national environmental hazards research centers. These centers are exploring the possible health consequences of military service in the Gulf War. Some projects are relatively small, while others involve thousands of participants.

Researchers are considering an array of possible causes including, but not limited to, oil well fires, vaccinations, infections, chemicals, pesticides, microwaves, depleted uranium, and chemical and biological warfare agents. All potential causes are receiving serious consideration and appropriate investigation. In 1996, VA established a fourth environmental hazards research center which is focusing on the possibility of reproductive problems related to military service.

A number of endemic and routine infectious agents have been investigated as potential causative agents for GW veterans' illnesses. In 1991, a small number of GW veterans returned from Southwest Asia with infectious diseases that have been diagnosed and treated. Infections with viruses, viscerotrophic leishmaniasis, mycoplasma, microsporidia, and nonculturable bacteria are among the agents some individuals have hypothetically linked but not conclusively shown to cause the illnesses of GW veterans. Extensive medical testing to date has not found an association link between the infectious agents and the illnesses GW veterans are now reporting. The Centers for Disease Control and Prevention (CDC) have reviewed the available evidence and has determined that at this time that there is no scientific evidence to suggest that illnesses among GW veterans are caused by infectious agents. Numerous research studies are underway to investigate this matter further.

Veterans and their families are concerned that the children of GW veterans may have an increased risk of birth defects. These fears have been fueled by anecdotal reports on birth defects in the popular media. While we do not now have a conclusive answer to this important question, this possibility is being thoroughly investigated. In January 1996, *Military Medicine* published the results of a small-scale study by investigators from the VA Medical Center in Jackson, MS, and the Mississippi State Department of Health. This collaborative research effort was conducted in response to a newspaper report of an apparent cluster of birth defects and other health problems among children born to veterans of two Mississippi National Guard units after their return from the Gulf War. The medical records of all children conceived by and born to veterans of these units after deployment were reviewed. Observed numbers of birth defects and other health problems were compared with expected numbers using rates from birth defect surveillance systems and previous surveys.

The total number of all types of birth defects was not greater than expected. However, because of the small numbers in this study, investigators could not determine whether the number of specific birth defects was greater, equal or smaller than expected. Investigators reported that the frequency of premature birth, low birth weight, and other health problems appeared similar to that in the general population.

In June 1997, *The New England Journal of Medicine* published a much larger study of the risks of birth defects among children of GW veterans. Researchers evaluated the routinely collected data on all live births at 135 military hospitals in 1991, 1992, and 1993. Records of more than 75,000 newborns were reviewed for any birth defect and for defects defined as severe on the basis of specific diagnoses and the criteria of the CDC.

During the study period, 33,998 infants were born to GW veterans and 41,463 to non-deployed veterans at these hospitals. Investigators found that the overall risk of any birth defect and the risk of severe defects was similar to those reported in civilian population. Furthermore, there was no significant association for either men or women between service in the Gulf War and the risk of any birth defect or of severe birth defects in their children (NEJM,1997;336:1650-1656).

The VA's national health survey of GW veterans and their families is in progress. Phase I is a survey of 15,000 GW veterans and a comparison group of 15,000 Gulf-era veterans who were not deployed to the theater of operations to assess prevalence of symptoms and medical conditions was completed in August 1996. Phase II consists of 8,000 telephone interviews and a review of 4,000 medical records. Phase III will involve physical examinations of veterans and their families. Investigators hope to learn a great deal about the problems experienced by the offspring of GW veterans from this survey.

In November 1996, VA established an Environmental Hazards Research Center at the VA Medical Center in Louisville, KY, specifically to focus research on the potential reproductive and development hazards of military service. The Center's overall goal is to determine whether exposures to hazardous substances affects reproductive capacity and causes developmental abnormalities in the children of veterans.

GW veterans have reported multisystem symptoms and been diagnosed with a wide spectrum of medical conditions, both diagnosed and undiagnosed. A CDC survey of GW veterans found that deployed GW veterans have a significantly increased rate of symptom reporting when compared to their non-deployed counterparts [MMWR, 1995 Jun 16;(23):443-447]. A large population based telephone survey of Iowa veterans showed that those deployed to the Gulf War have a higher prevalence of self-reported symptoms compared to the non-deployed veterans. Those symptoms include those consistent with depression, PTSD, chronic fatigue, cognitive dysfunction, bronchitis, asthma and fibromyalgia. Although the investigators identified potential relationships between the self-reported symptoms and exposures, there were no consistent patterns noted between the exposures and the health outcomes reported [JAMA, 1997;277(3):238-245]. However, Haley et al., in a study of the 24th Naval Reserve Construction Battalion, indicated that these self-reported symptoms could be aggregated by factor analysis into six distinct syndromes. The three most prominent syndromes were associated with exposures to pyridostigmine, pesticides, and possible chemical warfare agents. In the opinion of the investigators, these syndromes were suggestive of a possible neurologic basis for the symptoms [JAMA, 1997;227(3):215-237]. Serious limitations in these studies mitigate against drawing definitive conclusions from this work including non-representative sampling, small sample size, self-reported exposures, and in the later study, poor response rates. Follow-up investigations to this preliminary work are being planned.

Other investigators have also studied pyridostigmine bromide as a possible risk factor for development of health problems in GW veterans. Pyridostigmine bromide is a carbamate acetylcholinesterase inhibitor. Pyridostigmine bromide has been used as a nerve agent protective measure against organophosphate chemical warfare nerve agents. U.S. forces followed the doctrine of only using pyridostigmine bromide when a nerve agent threat was assessed to be imminent. On orders of a responsible division or corps-level commander, 30 mg pyridostigmine tablets would be taken orally every eight hours. Like nerve agents, carbamates inhibit the enzymatic activity of acetylcholinesterase (AChE). Unlike chemical warfare nerve agents, the

interaction between carbamates and the active site of AChE is spontaneously reversible. Carbamoylated AChE is protected from attack by nerve agents because the active site of the enzyme is not accessible to binding of nerve agent molecules. Pyridostigmine pre-treatment that results in carbamoylation of 20% to 40% of the AChE does not significantly impair neurotransmission or normal functioning of the soldier. Prompt post-exposure treatment with atropine and an oxime reactivator is needed for pyridostigmine bromide to be effective. Pyridostigmine has been used safely for many years in treatment of myasthenia gravis.

Studies of possible interactions of pyridostigmine administered together with the insect repellent diethyltoluamide (DEET) and the insecticide permethrin have demonstrated possible synergistic toxicity. The relevance of these reports to the experience of GW veterans is unknown since systemic administration of the interacting compounds was at least 10,000 fold in excess of the maximum potential exposure to U.S. troops in Operation Desert Storm. Low dose studies have been funded and are underway. A recent animal study found that stress may enhance the blood-brain barrier permeability of pyridostigmine bromide and enhance the resultant neuronal excitability [*Nature Medicine*, 1996;2(12):1382-1385].

War-related stressors are a unique human experience. During Operations Desert Shield and Desert Storm, in addition to the experience of being in actual combat, U.S. troops experienced many other forms of stress, including short deployment notice, family and employment-related concerns, uncertainty about the length of the deployment, environmental exposures, poor living conditions, anticipation of a high casualty and death rate, casualties and dead bodies, and the constant threat of chemical and biologic warfare attack. Post-deployment also resulted in stressful conditions for returning forces. Acute stress reactions and posttraumatic stress disorder are not the only conditions that arise after wartime experiences. Based on years of clinical observation and scientific study, it is recognized that stress may have physical as well as psychological consequences. Stress is known to affect the endocrine, immune, cardiovascular and nervous systems. For this reason, the Presidential Advisory Committee concluded in its final report that stress "…is likely to be an important contributing factor to the broad range of physiological and psychological illnesses currently being reported by Gulf War veterans."(ISBN 0-16-048942-3, 1997).

A DoD study of the post-war hospitalization experience of GW veterans [NEJM, 1996; 335 (20):1505-1513] indicates that, at least among active duty personnel, the rate of hospitalizations of GW veterans does not exceed the hospitalization rates in their non-deployed counterparts. This suggests that GW veterans are not experiencing an excess of illnesses of a severity that would lead to hospitalization. Caution must be exercised, however, in drawing a more general conclusion because the study does not account for veterans who may have left the military, nor does it account for individuals who are hospitalized in nonmilitary facilities.

In the remainder of this chapter, research studies published related to the health risks and illnesses of GW veterans are summarized.

5A: Mortality Study

Reference: ***Mortality Among U.S. Veterans of the Persian Gulf War***
New England Journal of Medicine. 1996;335(20):1498-1504.

Authors: Han K. Kang, Dr.P.H., and Tim A. Bullman, M.S., Department of Veterans Affairs, Environmental Epidemiology Service, Washington, DC

Background

Since the 1990-1991 Gulf War, there has been concern that U.S. war veterans may have experienced adverse health consequences, including increased mortality due to external causes (motor vehicle accidents and accidents of other types, suicide, and homicide). The authors conducted a retrospective cohort study of mortality in which they compared the postwar mortality of GW veterans with that of veterans from the era of the Gulf War who did not serve in that conflict. This study complements the DoD study of non-battle related deaths among GW troops who remained on active duty.

Methods

The study subjects were all 695,516 military personnel who served in the Gulf War area from August 1990 to April 1991. A control group of 746,291 military personnel consisted of a stratified random sample of approximately half of all personnel on active duty in the National Guard and in the military reserves who served from September 1990 to April 1991 but did not go to the Gulf. The vital status of each GW veteran from the date the veteran left the Gulf area was determined with a VA database. Death certificates were obtained and causes of death were coded. The data obtained were analyzed in three stages:

1. the relative frequency of death overall, as well as death due to specific causes, was compared between the GW veterans and the controls on the basis of the number of person-years at risk;
2. the Cox proportional-hazards model was used to account for possible confounding and the effect of selected covariates on the risk of a veteran's dying from a specific cause, according to the time since that veteran's entry into the cohort; and
3. the cause-specific mortality of GW veterans and other veterans was compared with the number of deaths expected in the overall U.S. population after adjustment for age, sex, race, and year of death.

Results

The demographic and military characteristics of the GW veterans were similar to those of the controls with the exception of the year of birth, sex, and type of unit. After controlling for potential confounders (age, sex, race, and military variables), the GW veterans had significantly higher mortality from all causes than the other veterans. The excess deaths were entirely attributable to external causes, including all types of accidents and motor vehicle accidents. There was no observed excess of suicides, homicides, or deaths from disease-related causes. The risk of death from infectious and parasitic diseases was significantly lower among the GW veterans than among the other veterans.

Relative-risk estimates derived from the Cox proportional-hazards model showed that overall mortality and mortality from all external causes, including accidents of all types and motor vehicle accidents, continued to be significantly elevated among the GW veterans as compared with the controls. In men, the risk of disease-related mortality was lower among GW veterans than among controls. The effect of being mobilized without being sent to the Persian Gulf did not appear to affect the overall mortality or the risk of death from external causes, even after adjustment for the type of unit, age, sex, race, and branch of service. As compared with the general population of the United States, the GW veterans and the non-GW veterans both had significantly lower cause-specific standardized mortality ratios. Deaths

among both groups of veterans occurred at a rate no more than half that expected in the U.S. population after adjustment for age, sex, race, and year of death.

Women sent to the Gulf War area also had a significant excess of deaths from all external causes, including accidents. The adjusted rate ratio was higher among female than among male veterans. In contrast, the rate ratio for deaths from disease-related causes was almost the same among female veterans as among male veterans. Being mobilized without actually serving in the Persian Gulf areas appears to have affected the mortality rates of women more than those of men. Women who were deployed somewhere (but who did not serve in the Gulf) had a higher, but not a significantly higher, rate of death from all causes than non-mobilized women, a higher rate of death from external causes, and a higher rate of death from accidents after adjustment for the type of unit, age, race, and branch of service. Female GW veterans had a higher (but not significantly higher) risk of death from external causes, including accidents, than their female peers in the general U.S. population. The rate of death among the female GW veterans was 43 percent higher than expected, whereas among other female veterans the risk was 31 percent lower than expected.

Discussion

GW veterans have had a significantly higher mortality than other veterans who served during the same period. Accidental deaths accounted for most of this increase. Neither the suicide rate nor the homicide rate was elevated among GW veterans. Mortality due to illness was not higher in GW veterans than in other veterans. The significant excess mortality from external causes among GW veterans as compared with controls is similar to what has been observed in studies of veterans of other wars. The underlying reasons for the excess of deaths due to external causes among war veterans are not well understood.

The authors note that serious flaws in the design and execution of the study are an unlikely explanation for their findings. To minimize statistical variation due to sampling, the study included all GW veterans and almost half of all military personnel who were not sent to the Persian Gulf. The interpretation of the study findings is somewhat confounded by the possibility that military personnel who were seriously ill or recovering from major surgery would not have been deployed to the Persian Gulf area. Another limitation of the study is the reliance on death certificates rather than medical records for information on causes of death. A further possible limitation is the lack of data on potential risk factors, such as a history of smoking and/or drinking, and preexisting mental disorders.

The effect of the Gulf War on postwar mortality appears to be greater among female veterans. Both male and female veterans of the conflict had higher rates of mortality from external causes than the controls, but the increase was greater among women. In contrast, there was no excess of deaths from disease among either male or female GW veterans. Mobilization without actual service in the Persian Gulf area had no substantial effect on the mortality of GW veterans as a group. Among women, however, those who were mobilized had a higher risk of death from each category of external causes than those who were not mobilized, although the risk was not significantly higher.

In summary, as compared with non-GW veterans, veterans of the conflict in the Persian Gulf had significant excesses of death from external causes (mainly accidents), but not from disease-related causes. Their risk of death remained less than half that expected in their civilian counterparts. The findings are consistent with the postwar mortality observed in veterans in previous wars.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5B: Morbidity Studies

Reference: ***The Postwar Hospitalization Experience of U.S. Veterans of the Persian Gulf War***
New England Journal of Medicine. 1996;335(20):1505-1513.

Authors: Gregory C. Gray, Bruce D. Coate, Christy M. Anderson, Han K. Kang, S. William Berg, F. Stephen Wignall, James D. Knoke, Elizabeth Barrett-Connor

Background

Since the Gulf War ended in 1991, many veterans of that conflict have reported diverse, unexplained symptoms. Thus far, clinical evaluations have not implicated specific exposures or a recognized disease process as causing the multiple symptoms, nor have they identified a new illness. To evaluate the health of GW veterans, the authors studied veterans' post-war hospitalization experience and compared it with that of other military personnel serving at the same time who did not go to the Persian Gulf.

Methods

The authors used a retrospective cohort approach and data from Department of Defense hospitals to study the hospitalizations of 547,076 veterans of the Gulf War who were serving in the Army, Navy, Marine Corps, and Air Force and 618,335 other veterans from the same era who did not serve in the Gulf War. The hospitalization records included up to eight discharge diagnoses which were coded by using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). For this report, multivariate logistic-regression models were used to analyze the risks for overall hospitalization and hospitalization for a diagnosis in each of 14 broad ICD-9-CM categories (not including diagnoses involving the reproductive system) for three periods from August 1991 through September 1993 (a total of 45 comparisons).

Results

GW veterans were at slightly lower risk of hospitalization for any cause than other veterans two years before the war, but the risk did not differ after the war. The odds of hospitalization due to diagnoses in the ICD-9-CM categories differed between the two cohorts with GW veterans at greater risk in five models: neoplasms (in 1991), diseases of the genitourinary system (in 1991), diseases of the blood and blood-forming organs (in 1992), and mental disorders (in both 1992 and 1993). The ten most frequent diagnoses in each of the five models accounted for 68 to 100 percent of the diagnoses in their respective categories:

1. The 10 most frequent discharge diagnoses involving neoplasms in the last five months of 1991 were mostly for benign conditions and showed no significant difference in rates between GW veterans and other veterans. The one exception was testicular cancer, but the event was rare and GW veterans were not hospitalized significantly more often with this diagnosis than other veterans in 1992.
2. Female GW veterans were at slightly greater risk for hospitalization for disorders of the genitourinary system than other female veterans during the last five months of 1991. Specifically, they were at increased risk for inflammatory diseases of the ovary, fallopian tube, pelvic cellular tissue, and peritoneum and for infertility.
3. Male GW veterans were at slightly higher risk of hospitalization than other male veterans for redundant prepuce and phimosis, a diagnosis often associated with hospitalization for circumcision.
4. Both male and female GW veterans were at slightly increased risk of being hospitalized for "other disorders of the breast," a nonspecific diagnosis.
5. Hospitalizations in 1992 for diseases of the blood and blood-forming organs were usually for anemia. However, when pregnancy-related

hospitalizations (as a result of a postwar baby boom among GW veterans) were removed from consideration, the resulting values showed no increase in risk among GW veterans. This suggests that the increase in risk was primarily due to anemias associated with pregnancy.

6. Finally, the 10 most frequent diagnoses of mental disorders in 1992 and 1993 were examined. GW veterans were hospitalized significantly more often than other veterans for conditions related to alcohol and drug use and for adjustment reactions.

Discussion

Comparisons between the two groups in this study yielded few surprises. The increased overall risk of hospitalization among women is consistent with the findings of a previous study of hospitalizations in the Navy. The increased rates of hospitalization after the war for conditions related to drug and alcohol use and adjustment reactions have been reported in other groups of combat veterans. Finally, the comparisons of separation rates are consistent with the results of other recent mortality studies that have not shown GW veterans to have a higher overall or disease-related risk of death than other veterans.

The prewar selection effect is understandable in that the services permit recently hospitalized personnel to remain attached to their operational units while they convalesce, but the limited-duty status of these personnel makes them ineligible for deployment. The data suggest that this selection effect is transient and that the reduction in the risk of hospitalization seen before the war disappeared shortly after the war. After a prewar-hospitalization covariate was created to control for this selection effect in the multivariate models, the odds ratios in the two cohorts remained essentially the same.

Some differences were found in the risks associated with specific diagnostic categories and rates of specific diagnoses. These differences were not consistent over time and do not suggest an emerging illness associated with GW service. Many of the observed differences between cohorts with regard to rates of diagnoses suggest that medical care for some conditions was deferred until after the war. This is true with regard to the diagnosis of redundant prepuce and phimosis, which usually means that elective circumcision was performed. Deferred diagnostic evaluation or surgery probably also accounts for the slight increases in the rates of various benign neoplasms and of hospitalizations for inflammatory disease or infertility in women that occurred immediately after the war. Because no known associations between an exposure and the appearance of a neoplasm have such a short latency period and because women are hospitalized for infertility only after months, if not years, of outpatient medical care, it is difficult to implicate GW service in causing these conditions. It is more likely that GW veterans waited until they were home before undergoing elective hospitalization.

In conclusion, the authors constructed multivariate logistic-regression models for hospitalization both overall and for conditions assigned to any of 14 broad diagnostic categories in each of three postwar periods. The risk associated with 16 of these 45 comparisons differed between GW veterans and other veterans. In five of these 16 cases, the risk of hospitalization was higher among GW veterans, but the increases were inconsistent over time and were probably due to deferred medical care, a post-war baby boom, chance, or mental conditions known to be associated with war. The data suggest that GW veterans who remained on active duty were not at increased risk for unexplained hospitalization during the 25 months after the war.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5C: Reproductive Outcomes

Reference: ***The Risk of Birth Defects Among Children of Persian Gulf War Veterans***
New England Journal of Medicine. 1997;336:1650-1656.

Authors: David N, Cowan, Ph.D., M.P.H., Robert F. DeFraites. M.D., M.P.H., Gregory Gray, M.D., M.P.H. Mary Goldenbaum, M.L.S., Samuel M. Wishik, M.D., M.P.H.

Introduction

During the six years since the Gulf War, there has been concern that the veterans health was adversely affected, and there have been claims that the children of GW veterans suffer from an increased rate of birth defects. This study found no evidence of an increase risk of birth defects among the children of GW veterans.

Methods

Of the 696,562 military personnel deployed for at least one day to Operations Desert Shield and Desert Storm from August 8, 1990 to July 31, 1991, 579,931 were active duty members of the Army, Navy, Air Force or Marine Corps and were considered eligible for inclusion in the study. A comparison group composed of 700,000 service members who were not deployed to the Gulf region—approximately half of all such personnel—was selected from the total population of military personnel. Reservists were excluded, since neither they nor their dependents were eligible for care in military hospitals after the military member was released from active duty. Military data on administration, demographics and hospitalization were obtained from the Department of Defense databases.

For GW veterans, all live births that occurred before October 1, 1993, with an estimated conception date after return from the Gulf region were included. For the comparison non-deployed group, all live births that occurred before October 1, 1993, with an estimated conception date after December 31, 1990 were included. Hospitalization data included up to eight diagnoses coded to five digits by the medical records personnel using the International Classification of Diseases, 9th revision, Clinical Modification (ICD -9-CM). Data on babies included sex and birth date but did not include birth weight or gestational age. Births paid for by the military that occurred in civilian facilities were identified and used for estimates of fertility and total number of live births.

The primary outcome assessed in the study was the occurrence of birth defects. Two secondary outcomes were also analyzed: the number of live births per 1000 population and the ratio of male to female babies. "Birth defects" for the purposes of this study were defined in two ways. First, a very sensitive definition of "any birth defect" as defined by the Metropolitan Atlanta Congenital Defects Program which includes virtually all ICD-9-CM codes related to congenital malformations (740 to 759), as well as neoplasms and hereditary diseases. The second definition, "severe birth defects," was based on the specific defects considered by the CDC to be frequent and severe enough to represent a public health problem.

Exposure was defined only as deployment to the Gulf region. Deployment was analyzed by three-month increments in the duration of deployment and as a continuous variable based on the number of days of deployment.

Results

A total of 543,541 male and 35,164 female GW veterans and 613,762 male and 86,192 female nondeployed veterans were included in the study. Of the identified births that occurred during the study period, 58% of the births of wives of male GW veterans and 7% of the births of wives of male nondeployed veterans occurred in military hospitals. Essentially all (over 99%) of the live births to female service members occurred in military medical facilities. There were 30,151 children born in military hospitals to the wives of 29,468 male GW veterans and 32,638 born to the wives of 31,646 non-deployed veterans. Among

women service members, 3,847 live births occurred in 3,722 GW veterans and 8,825 to 8,494 non-deployed veterans. Male GW veterans were about one year younger on average than their non-deployed counterparts at the time of their child's birth. Male and female GW veterans were significantly more likely than the non-deployed veterans to be single, black, in the Army, and of enlisted rank. Female GW veterans were, on average, about seven months younger than the non-deployed veterans and six months younger at child birth.

Among the men identified in the original population, the rate of live births was 95.4 per 1000 for deployed and 93.29 per 1000 for non-deployed veterans. Among women the rates of live births were 109.40 per 1000 and 102.39 per 1000 for deployed and non-deployed veterans, respectively. Significantly more births occurred for male and female GW veterans than for non-deployed veterans. In addition, the male to female ratios for the children of GW veterans were not found to be significantly different than the children of non-deployed veterans.

For male service members, no positive association was identified between GW service and the risk of any birth defect. However, among female veterans, there was a statistically significant increase in risk of birth defects for Gulf veterans, with a relative risk of 1.12(95% CI, 1.00 to 1.25). After adjustment for marital status, race or ethnicity, and branch of service, there was no significant association between GW service and the risk of birth defects, suggesting that the univariate association could be due to confounding. No linear trend of increasing risk with increasing time spent in the Gulf region was demonstrated in this study. Nor was there any change in risk associated with the interval between return from the Gulf region and the babies' date of birth. Moreover, there was no significant association between GW service and risk of severe birth defects for the children of either male (RR = 1.03, 95% CI = 0.92 - 1.15) or female (RR = 0.92, 95% CI = 0.90 - 1.10) veterans.

Discussion

The study was designed to test the hypothesis that children born to GW veterans were at increased overall risk of birth defects. The study findings do not support that hypothesis, since most of the univariate relative risks and all of the adjusted odds ratios were close to 1.0. While the risk of any birth defect was slightly higher among the children of female GW veterans, this finding appears to be the result of confounding by race or ethnicity, marital status, and branch of service. The risk of birth defects in both the deployed and the non-deployed military populations approximated the risk in a civilian population.

This study has some definable limitations. Only children born in military hospitals were included which accounts for approximately 68% of all the births to active duty military personnel during the study period. Births to reserve component members or individuals who left active duty before the study period were excluded. Only birth defects evident at birth and coded on the birth discharge summary were included. Diagnoses made subsequently or in nonmilitary settings were not analyzed.

Despite these limitations, the findings of this study provide substantial evidence that the children of GW veterans do not have an increased risk of birth defects. In addition, there is no evidence for decreased fertility in GW veterans and there are no significant differences in the sex ratios of babies of GW veterans.

Note: A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."

5C: Reproductive Outcomes

Reference: ***No Evidence of Increase in Birth Defects and Health Problems among Children Born to Persian Gulf War Veterans in Mississippi***
Military Medicine. 1996 Jan;161(1):1–6.

Authors: Alan D. Penman, Bureau of Preventive Health, State Department of Health, 2423 North State Street, Jackson, MS 39215; Russell S. Tarver, Department of Veterans Affairs Medical Center, 1500 East Woodrow Wilson, Jackson, MS 39216

Background

In late November 1993, the local Jackson, Mississippi, newspaper reported an apparent cluster of birth defects and other health problems among children born to veterans of two Mississippi National Guard units after their return from the Gulf War. According to the wife of one veteran, 12 children out of 15 were affected. A variety of reported birth defects and health problems was reported, but detailed information was not immediately available.

From December 1993 through May 1994, the Department of Veterans Affairs, Jackson, Mississippi, the Mississippi State Department of Health, and the Centers for Disease Control and Prevention conducted a collaborative investigation to determine whether an excess number of birth defects occurred among children born to this group of veterans and, if so, whether etiologic/pathologic patterns in the birth defects could be observed.

Methods

Mississippi has approximately 5,000 National Guardsmen in 124 National Guard units; 65 of these units were mobilized for the Gulf War, and approximately 1,000 personnel were sent to the Middle East. The reported cases of birth defects and health problems in children came only from veterans in two units based in southeast Mississippi. Therefore, the survey was restricted to all of the service personnel from these two units. Of 282 veterans in the two units, initial phone contact was made with 254 (90%). The remaining 28 had left the National Guard and could not be contacted. In this group, 67 veterans or their spouses gave a history of pregnancy since return from deployment in the Gulf War.

Because the veterans and their spouses/significant others were concerned about birth defects, premature births, and other health problems in their children (e.g. respiratory infections, otitis media, blood disorders, and jaundice), the medical records of all children conceived by and born to veterans of the two units after deployment were reviewed. Of the 54 births for which medical records were obtained, 29 (54%) were male, and 30 (56%) were white. As of May 1994, the ages of the children ranged from three to 26 months. Maternal ages ranged from 18 to 41 years (mean 25). The mother was the veteran in six of the families, including one family in which both parents were veterans.

Standard case definitions for birth defects, low birth weight, and premature birth were used, but diagnoses written in the medical records were accepted. A case was defined as a serious structural congenital malformation diagnosed during the first year of life. A serious malformation was one that could be associated with premature death, cause substantial handicap, or require surgery or extensive medical care. Any structural congenital malformation not meeting the previous definition was classified as a minor birth defect. A case of low birth weight was defined as a birth weight of less than five pounds, eight ounces. A premature birth was defined as birth of an infant at less than 37 weeks gestation.

To obtain baseline rates for comparison, data were used from the three major U.S. birth defect surveillance systems that survey segments of the general population. Because many of the families expressed concern about the high frequency of non-congenital health problems in their children, the authors compared the observed numbers of some of these conditions in this group with the

numbers expected using rates from published studies or generally accepted rates.

Results

Three cases of major birth defect were found: one case of craniosynostosis and perimembranous ventricular septal defect in an infant born at 37 weeks gestation; one case of posterior urethral valves with hydronephrosis in a full-term infant; and one case of bilateral trigger fingers in a full-term infant. Two cases of minor birth defect were found: one case of pulmonary stenosis that was judged to be hemodynamically insignificant and one case of single umbilical artery without associated abnormalities. No stillbirths or deaths were noted.

Five cases of low birth weight were observed. Multiple other conditions occurring in the post-neonatal period were reported by the parents in the telephone survey or noted in the clinical records. The number of cases of each condition or problem was minimal. A total of 38 children had a mean of 2.3 office visits for upper respiratory infection in the first year of life. A total of 26 children in this group made an average of 2.1 office visits for otitis media during the first year of life.

Discussion

The frequency of premature birth and/or low birth weight in the study group when compared with that of other groups should be interpreted with caution because:

1. The study could not account for confounding by all the well-known factors that can increase the risk for conceiving and giving birth to an infant with a congenital malformation.
2. The small size of the study population and the occurrence of only one case of each of five different types of birth defects (i.e. three major and two minor) makes the calculation of individual rates for the purpose of comparison difficult.
3. Low birth weight is associated with an increased frequency of congenital abnormalities, but none were observed among the low birth weight babies in this group.
4. The amount of morbidity from respiratory infections and otitis media observed during the first year of life in this group of children was not excessive.
5. Diagnoses stated in the medical records were accepted without further verification. However, with few exceptions, no major discrepancies were noted between the health problems reported by the parents and the diagnoses recorded by the physicians or, in the cases of those children referred for further investigation/surgery, between physicians.
6. The lack of data concerning the 28 families who could not be contacted is a possible source of bias. No information could be obtained on how many births occurred in this group nor what the outcomes were. If this nonparticipant group had healthy children, their omission from the study would make the observed rates higher than they actually were.

Conclusions

The authors found no increase in the total number of all types of birth defects among children conceived by and born to this group of GW veterans after deployment (i.e., the rate of birth defects of all types in children born to this group of veterans was similar to that expected in the general population). However, because of the small numbers involved, the authors could not determine whether the occurrence of any specific birth defect observed among this group of children differed from what was expected. Perhaps the most significant finding was that a variety of birth defects was observed, and clustering of any one type or affected system did not occur. Furthermore, no known genetic or chromosomal abnormality or teratogen was common to the various defects.

Note: A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."

5D: Infectious Diseases

Reference: ***The Impact of Infectious Diseases on the Health of U.S. Troops Deployed to the Persian Gulf During Operations Desert Shield and Desert Storm***
Clinical Infectious Diseases. 1995 June;20(6):1497–1504.

Authors: Kenneth C. Hyams, Kevin Hanson, F. Stephen Wignall, Joel Escamilla, Edward C. Oldfield

Summary

An assessment was conducted of the impact of infectious diseases on the 697,000 U.S. troops deployed to the Persian Gulf during 1990–1991 in Operations Desert Shield and Desert Storm. Published reports and data were obtained from the U.S. Navy's weekly surveillance system of outpatient visits among approximately 40,000 Marine Corps ground troops deployed to northeastern Saudi Arabia. As indicated by statistical data, the disease nonbattle injury rate, which includes infectious diseases, was lower during this military campaign than in any major war involving U.S. military personnel. Nondisabling acute enteric and respiratory infections, however, were a frequent occurrence.

Gastroenteritis

Diarrheal disease was the leading cause of infectious disease morbidity among U.S. troops. At the beginning of the rapid buildup of troops when the weather was very hot, outbreaks of acute diarrhea were common, and more than 50% of the troops in some initially deployed units reported an epidemic of acute diarrhea. The major risk factor for diarrheal disease among initially deployed ground troops was consumption of fresh fruits and vegetables obtained from neighboring countries. Viral gastroenteritis also was a cause of morbidity among troops, but no confirmed, acute case of cholera, typhoid fever, amoebic dysentery, or giardiasis was reported among troops.

Respiratory Disease

Acute, common cold-type respiratory complaints were a widespread cause of minor morbidity during both Operations Desert Shield and Desert Storm especially during periods of initial deployment and crowding. A major concern was that respiratory disease would result from exposure to the sand in this region. A survey of 2,598 U.S. troops, however, indicated that upper respiratory symptoms, other than chronic rhinorrhea, were most common among the minority of troops who resided in air-conditioned buildings.

Leishmaniasis

To date, 12 cases of visceral and 20 cases of cutaneous leishmania infection have been reported among U.S. GW veterans who were deployed to Saudi Arabia, Kuwait, and southern Iraq. Leishmania tropica was found in cases of visceral disease and Leishmania major in cutaneous cases in which parasites could be cultured and evaluated. There are several possible reasons for a low number of cases of cutaneous and visceral leishmaniasis:

1. insecticides and repellents were used against arthropod vectors in areas where group troops were camped;
2. most combat troops were stationed in the open desert rather than in oases or urban areas where the sandfly vector and the primary *leishmania* host, desert rodents, thrive; and
3. the troop buildup did not occur until the cooler winter season which is the lowest period of sandfly activity.

Other Arthropod-Borne Infections

No outbreak of febrile disease consistent with sandfly fever or other arthropod-borne disease was reported or observed in the U.S. Navy disease surveillance system of 40,000 Marine Corps personnel. The reasons why U.S. troops were at low risk of sandfly fever may be related to the low

number of cases of leishmaniasis because these two diseases are transmitted by the same sandfly vector. Use of insecticides and limited sandfly activity during the cold winter months, when most troops were deployed, would have lessened the risk of transmission of both diseases. Furthermore, because of differences in geographic location, the risk of sandfly fever may not have been as great for Desert Storm troops who were deployed in the open deserts of Saudi Arabia. The low occurrence of arboviral infections and leishmaniasis indicated a very low risk overall of arthropod-borne diseases.

Other Infectious Diseases

Infectious diseases that historically have plagued military populations--malaria, sexually transmitted diseases, and viral hepatitis—were not a problem during this deployment. Only seven cases of malaria were reported; STDs were an infrequent finding because of very limited contact between U.S. troops and other populations; and only a few cases of Hepatitis A and B were observed. No diagnosis of brucellosis and only three cases of *Coxiella burnetii* infection, which are endemic in the Middle East, have been reported. There have been no reported cases of schistosomiasis, echinococcosis, or active tuberculosis, but there were two cases of meningococcal disease.

Unexplained Illnesses

Since the end of the Gulf War, several thousand veterans from widely diverse military units have complained of chronic nonspecific symptoms, which have not been readily explained. The most common complaints have been chronic fatigue, headache, muscle and joint pain, shortness of breath, intermittent diarrhea, cough, and neuropsychological complaints, including sleep disturbance, difficulty concentrating, forgetfulness, irritability, and depression. No documented fever, characteristic skin rash, or consistent abnormality in results of laboratory tests currently have been identified. A number of possibilities have been considered as causes of these unexplained illnesses: various infectious diseases (e.g. visceral leishmaniasis, brucellosis, Q fever, Lyme disease, tuberculosis, and retroviral infections); biological warfare agents; an unknown or emerging infectious disease; and chronic fatigue syndrome. Because most veterans became ill several weeks to more than a year after returning to the U.S. (rather than after an illness while in the Persian Gulf) epidemic neuromyasthenia is considered an unlikely explanation for chronic fatigue and other generalized symptoms.

Conclusion

The fact that infectious diseases were not a major cause of lost manpower, unlike the experience of Western troops in the Persian Gulf during World War II, can be attributed to a combination of factors: the presence of a comprehensive infrastructure of medical care, extensive preventive medicine efforts, and several fortuitous circumstances, principally isolation of troops in barren desert locations and cooler winter conditions during the height of the troop buildup. Although U.S. troops were at low risk of incapacitation from infectious diseases during the Gulf War, other military campaigns may not be so fortunate. Chance events (e.g. time of year and geographic location of deployment) can have a major impact on the risk of transmission of infectious diseases and result in higher morbidity among deployed troops. The U.S. military must continue to support an aggressive program of preventive medicine, which is guided during deployments by continuous disease surveillance and on-site laboratory analyses. In addition, it is critical for the military to maintain an infectious diseases research program to develop new vaccines, improved medical treatments, and more accurate and rapid diagnostic tests.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5D: Infectious Diseases

Reference: ***Assessment of Arthropod Vectors of Infectious Diseases in Areas of U.S. Troop Deployment in the Persian Gulf***
American Journal of Tropical Medicine and Hygiene. 1996 Jan;54(1):49-53.

Authors: Stanton E. Cope, George W. Schultz, Allen L. Richards, Harry M. Savage, Gordon C. Smith, Carl J. Mitchell, David J. Fryauff, Joseph M. Conlon, Jeffrey A. Corneil, Kenneth C. Hyams

Background

Beginning in August 1990, approximately 800,000 coalition troops were deployed to the Persian Gulf during Operations Desert Shield and Desert Storm. There was substantial concern that coalition troops would be adversely affected by arthropod-borne infectious diseases, particularly sand fly fever and cutaneous leishmaniasis, because of high morbidity rates in the Persian Gulf during World War II. In sharp contrast to WWII, however, there were no reports of sand fly fever among coalition forces and only 31 cases of leishmaniasis among 697,000 U.S. troops. Consistent with the low incidence of arthropod-borne diseases the suspected vectors of the agents for these diseases appeared to be scarce in areas where coalition troops were deployed.

To determine the reason why troops were at low risk of arthropod-borne diseases and to further evaluate the risk of infection for troops who are currently deployed in this region, an entomologic survey was conducted between January and September, 1992, in 12 areas of U.S. troop deployment in Kuwait and Saudi Arabia.

Materials and Methods

The survey was conducted in 12 locations (four in Kuwait and eight in Saudi Arabia) where U.S. military personnel were located in 1992. The 12 sites were chosen based on diversity of ecologic conditions, the presence of U.S. troops, and accessibility. In Kuwait, all survey areas were near the Persian Gulf coast and in Saudi Arabia, sites 5-10 were near the Persian Gulf coast, and sites 11 and 12 were inland adjacent to the city of Riyadh.

Four collecting trips were made during 1992. Sand flies were collected using oiled-paper traps; mosquitoes, sand flies, and other host-seeking dipterans were collected using CDC light traps. Tweezers were used to collect host-seeking ticks from the desert floor. Ticks were also collected from trapped rodents. Vials containing cryopreserved sand flies were rapidly thawed in warm water. Female sand flies were examined under a dissecting microscope on a sterile glass slide in a drop of sterile PBS for the presence of promastigotes.

In addition to these collections, rodents were also captured and combed for ectoparasites and carefully examined for Leishmania lesions. Rodent sera were tested for antibodies to *Rickettsia conorii* and *R. typhi*.

Results

A total of 1,556 arthropods was collected. Mosquitoes accounted for 78.7% (1,224) of collected arthropods, sand flies for 15.2% (236), *Culicoides* for 3.6% (56), and ticks for 2.4%. Six species of mosquitoes were identified, eight species of sand flies, at least one species of *Culicoides*, and three species of *Hyalomma* ticks.

The majority (87%) of specimens was collected during the hot, late summer period in August and September, 1992. The largest number of sand fly specimens were collected from the coast of Kuwait, whereas mosquitoes were found both along the coast and further inland around Riyadh. A total of 856 arthropods was processed in 50 pools for virus isolation; all pools were negative by plaque assay in Vero cell culture. Due to the

small numbers collected, only 25 sand flies were dissected for evidence of Leishmania infection; all were negative.

Among 52 captured mammals, there were 35 *Mus musculus*; eight *Gerbillus* species; eight *Meriones crassus*; and one hedgehog. The rodents appeared healthy and few ectoparasites were found; no external lesions were noted. There was no serologic reactivity to *R. conorii* or *R. typhi* antigen preparations among the captured rodents.

Discussion

The survey demonstrated the presence of the principal sand fly vector in areas of U.S. troop deployment in Kuwait and Saudi Arabia. In addition, the suspected mosquito vectors of the West Nile and Rift Valley fever, and the tick vector of Crimean-Congo hemorrhagic fever were detected. However, there was no evidence of arboviruses or *Leishmania* among collected arthropod vectors and trapped rodents.

Due to the limited extent of the survey and the focal nature of vectors and animal hosts of infectious agents, the risk of arboviral and *Leishmania* infection could not be estimated from the results of the survey. Although vectors of arthropod-borne disease agents were found in numerous locations, the low incidence of these infectious diseases among more than 500,000 coalition ground troops indicate that the risk was very low during Operations Desert Shield/Storm.

There are several possible reasons for the low risk of arthropod-borne infectious diseases among GW troops in an area where suspected vectors frequently were found:

1. the use of insecticides, repellents, and other protective measures would have lessened the risk;
2. most combat troops were deployed to the open desert where sand fly activity and host rodents are minimal; and
3. most troops were deployed during the cooler, winter period when sand fly and mosquito activity is lowest.

Reports of *L. tropica* infection causing mildly symptomatic visceral disease (viscerotropic leishmaniasis) among 12 U.S. GW veterans, however, were unexpected. Although there have been scattered reports of visceral *L. tropica* infection, this disease has not been reported previously in Saudi Arabia and Kuwait. The species of sand fly that serves as a vector of viscerotropic leishmaniasis has not been determined. A likely candidate is *P. sergenti*; however, this species was not found in this survey.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5D: Infectious Diseases

Reference: ***Visceral Infection Caused by Leishmania tropica in Veterans of Operation Desert Storm***
New England Journal of Medicine. 1993 May 13;328(19): 1383-1387.

Authors: Alan J. Magill, M.D.; Max Grogl, Ph.D.; Robert A. Gasser Jr., M.D.; Wellington Sun, M.D.; Charles N. Oster, M.D.

Background

Visceral leishmaniasis (kala-azar), usually caused by *Leishmania donovani*, has rarely been reported from eastern Saudi Arabia, so it was not expected to affect the soldiers of Operation Desert Storm. Kala-azar presents as a chronic febrile illness with emaciation, marked hepatosplenomegaly, pancytopenia, and hyperglobulinemia. In this article, the authors described eight American soldiers who had a systemic leishmanial infection that differed from kala-azar in that the infected organism was *L. tropica* rather than *L. donavani*. These patients did not have the classic signs or symptoms of kala-azar.

Methods

The authors evaluated eight soldiers with visceral leishmania infection. Patient One was evacuated from Saudi Arabia with an unknown febrile illness. Patients Two (abrupt onset of fever, rigors, nonproductive cough, and malaise one month after his return from Saudi Arabia), Three (onset of watery diarrhea, nausea, and diffuse abdominal pain two months after his return from Saudi Arabia), and Seven (sudden onset of fever, rigors, malaise, and right-lower-quadrant pain with diarrhea one month after returning from Saudi Arabia) were directly referred early in the course of their illnesses because of their symptoms. Patient Four was in the same unit as Patient Two, and his illness was diagnosed during a serologic survey. Patients Five and Six (gradual onset of malaise, fatigue, anorexia, nausea, abdominal pain, headaches, nonproductive cough, arthralgias, and myalgias seven months after returning from Saudi Arabia) were in the same unit as Patient One and were identified during a serologic survey. Patient Eight was referred because of a febrile illness.

Titers of antibody to leishmania were determined by immunofluorescence assays. Mononuclear cells obtained by density sedimentation of bone marrow aspirates were analyzed by an indirect immunofluorescence assay incorporating a monoclonal antibody specific for leishmanial organisms. Bone marrow samples were obtained from the iliac crest by needle aspiration. Cultured promastigotes were isolated and characterized by isoenzyme analysis.

Results

The patients with visceral leishmaniasis described in this article all presented between November 1990 and April 1992. Their median age was 32.5 years (range, 21 to 40), and all were males. For the maximal incubation period, defined as the interval between arrival in Saudi Arabia and the onset of symptoms, the median was seven months (range, two to 14); for the minimal incubation period, defined as the time between departure from Saudi Arabia and the onset of clinical illness, the median was two months (range, one to seven). In Patient One, the incubation period was two months since he became ill while in Saudi Arabia.

None of the eight soldiers had classic signs or symptoms of visceral leishmaniasis (kala-azar). Seven soldiers had unexplained fever, chronic fatigue, malaise, cough, intermittent diarrhea, or abdominal pain that began up to seven months after they returned to the United States; one had no symptoms. Five had adenopathy or mild, transient hepatosplenomegaly. None had cutaneous manifestations. Diagnoses were made by bone

marrow aspiration (seven patients) or lymph-node biopsy (one patient). Six isolates were identified as *L. tropica*, which usually causes only cutaneous disease. Of the six patients treated with sodium stibogluconate, five improved and one remained symptomatic.

No patient had lesions that suggested cutaneous leishmaniasis according to his history or physical examination. In the six patients in whom the infecting species could be differentiated, the leishmania were characterized as *L. tropica*. This organism has been reported to cause cutaneous leishmaniasis, but has rarely been reported to produce systemic illness. Six of the patients were otherwise healthy and immunocompetent. No other diagnosis was confirmed in these six patients despite extensive evaluations, and five of them responded to specific therapy for leishmaniasis. Patient Seven, who was HIV infected, had a nonspecific illness associated with HIV seroconversion. He was examined for leishmaniasis because of the high index of suspicion and an elevated titer. In Patient Eight, the localized renal-cell carcinoma was an unexpected finding during an exhaustive evaluation. Acute retroviral seroconversion and renal-cell carcinoma could explain the illnesses seen in these two patients, and the authors could not conclude that their clinical presentations were due solely to leishmaniasis. Visceral leishmaniasis was included in the differential diagnosis of systemically ill soldiers because it is one of the endemic infectious diseases of Saudi Arabia.

Discussion

The most severe clinical manifestation of visceral infection caused by leishmania is kala-azar, caused by *L. donovani. L. tropica* can produce visceral infection that can cause unexplained systemic illness in persons returning from areas where this organism is endemic. The finding of visceral illness due to *Leishmania* in returning troops raised at least two important clinical issues: late presentation due to prolonged incubation and activation of latent infection in immunosuppressed persons.

Leishmanial illnesses similar to those described here may not be recognized as such when they occur in populations in which they are endemic, because of their protean clinical manifestations, insensitive diagnostic tests, and infrequent examination of bone marrow for amastigotes. Another possibility is that nearly universal infection in childhood leads to resistance to disease in adult life. The exposure of more than 500,000 nonimmune adults during Operation Desert Storm may therefore have revealed more of the clinical spectrum of infection caused by *L. tropica*.

The authors describe a systemic illness caused by *L. tropica*. This illness is called "viscerotropic" leishmaniasis to distinguish it from "visceral" leishmaniasis. The natural history of this illness is not yet defined and the prevalence of infection among returning troops is not known. Diagnosis still requires an invasive procedure, such as a bone marrow aspiration or a lymph-node biopsy, and specialized laboratory support that is not widely available. This disorder should be included in the differential diagnosis of unexplained systemic illness in patients who have returned from areas of the world where leishmaniasis is endemic.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5E: Unexplained Illness/Symptoms

Reference: ***Unexplained Illness Among Persian Gulf War Veterans in an Air National Guard Unit: Preliminary Report August 1990–March 1995***
Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. 1995 Jun 16;44(23):443-447.

Background

In November 1994, the U.S. Department of Veterans Affairs (VA), the Department of Defense (DoD), and the Pennsylvania Department of Health requested that CDC investigate a report of unexplained illnesses among members of an Air National Guard (ANG) unit in south-central Pennsylvania (Unit A) who were veterans of the Gulf War (August 1990–June 1991). These veterans had been evaluated at a local VA medical center for symptoms that included recurrent rash, diarrhea, and fatigue.

A three-stage investigation was planned to:

1. verify and characterize signs and symptoms in GW veterans attending the VA medical center;
2. determine whether the prevalence of symptoms was higher among members of Unit A than among members of other units deployed to the Gulf War and, if so, whether the increased prevalence was associated with GW deployment; and
3. characterize the illness and identify associated risk factors. This report presented preliminary findings from stages one and two (stage three is in progress).

Stage One

In December 1994, a team of CDC medical epidemiologists visited the VA medical center, conducted standardized interviews and performed standardized physical examinations of 59 GW veterans reported to be asymptomatic, and reviewed medical records. Of the 59 veterans, 26 were selected from the health registry that had been established for GW veterans who reported symptoms believed to be related to service in the Gulf War, and 14 were selected as typical cases by the physician who reported the illnesses to VA; the remaining 19 were listed on the registry but had not yet been evaluated at the VA medical center to determine whether they were eligible to be on the registry. In addition, 40 primary care physicians and 16 regional hospitals in south-central Pennsylvania were surveyed; the survey did not identify additional GW veterans with any health complaints.

The median age of the 59 persons was 39 years (range: 23-59 years), and 53 (90%) were male. All were enlisted personnel: 30 (51%) had been assigned to Unit A during the Gulf War and the remainder were in other Air Force units and military branches; 48 (81%) had been in the military for 10 or more years; 16 (27%) had served for five or more years on active duty; and 19 (32%) had been deployed for 2 or more tours to the GW theater. At the time of the survey, 89% were employed in addition to their ANG work.

The most frequently reported symptoms considered "moderate" or "severe" were fatigue (61%), joint pain (51%), nasal or sinus congestion (51%), diarrhea (44%), joint stiffness (44%), unrefreshing sleep (42%), excessive gas (i.e. flatulence, bloating, and gastrointestinal distress) (41%), "difficulty remembering" (41%), muscle pains (41%), headaches (39%), abdominal pain (36%), general weakness (34%), and impaired concentration (34%). The two symptoms identified as "most bothersome" were fatigue (27%) and diarrhea (14%). Patients reported that their symptoms began during or two to three months after departure from the Persian Gulf, and all reported that several symptoms persisted for six or more months. No consistent abnormalities were identified among the participants on standardized physical examination or by review of medical

records and accompanying laboratory tests performed at the VA medical center. After the war, one participant had viscerotropic leishmaniasis diagnosed and treated.

Stage Two

From January through March 1995, members of Unit A and three comparison units (units B, C, and D) were surveyed to determine the prevalence of selected symptoms identified in stage one and to examine the relation between reported symptoms and GW service. Comparison units were chosen for similarity in mission responsibility to Unit A and were located in Pennsylvania and another state. Units B and C (both reserve units) were surveyed during routine monthly training sessions, and Unit D (an active duty unit) was surveyed immediately after the Unit C survey. All personnel on each base at the time of the survey were asked to participate, regardless of health status or participation in the Gulf War, by anonymously completing a questionnaire describing the frequency, duration, and severity of 35 symptoms most commonly mentioned during the stage one investigation and a general health history. In addition, personnel who had been deployed to the Persian Gulf were asked about possible exposures (e.g. geography [location of service], duties [combat or support], medical and other procedures [e.g.vaccinations, dental work], outdoor activities [sports, recreation, mission-related], and food and water sources).

A total of 3,927 personnel participated in the survey. Response rates varied by unit: 63% (677 of 1,083) in Unit A, 36% (540 of 1,520) in Unit B, 74% (843 of 1,141) in Unit C, and 78% (1,867 of 2,407) in Unit D. The distribution of demographic characteristics and deployment status of these study participants was similar to the distribution of these variables in the population of each unit.

In all units, the prevalence of each of 13 chronic (lasting six or more months) symptoms was significantly greater ($p < 0.05$) among persons deployed to the Gulf War than among those not deployed. The prevalence of five symptom categories—chronic diarrhea, other gastrointestinal complaints (gas, bloating, cramps, or abdominal pain), difficulty remembering or concentrating, "trouble finding words," and fatigue—were significantly greater ($p < 0.03$) among deployed personnel from Unit A than among deployed personnel from each of the other units. Prevalence of symptoms among non-deployed personnel were similar in all units.

Editorial Note

The preliminary findings of this investigation are subject to at least two limitations. First, the stage two data on symptom prevalence reflect self-reported information that was not evaluated by physical examination and laboratory tests. However, standardized physical examinations and review of VA laboratory test results from patients in stage one did not reveal consistent abnormalities. Second, participation rates for the stage two survey varied widely because persons with symptoms may have been more likely to participate; therefore, the prevalence of reported health conditions may have been over-estimated.

The preliminary findings presented in this report indicate that some chronic symptoms were reported more commonly by GW veterans than by nondeployed Gulf War-era service personnel. Potential explanations for the higher prevalence of symptoms among deployed personnel—and the increased prevalence among deployed personnel from Unit A—may include factors specific to the Persian Gulf region (e.g., environmental, toxic, and infectious exposures); factors related to military service and combat (e.g., exposure to toxic agents and combat-related disorders, age-related effects, or other poorly defined chronic illnesses); and factors especially specific to Unit A (e.g., increased local concern and media attention about illnesses related to GW service when compared with other units). The stage three case-control study in progress will assess risk factors in ill and healthy GW veterans from Unit A.

Mechanisms have been established to rapidly identify and treat GW veterans with health problems. All GW veterans with health problems are encouraged to obtain an evaluation at their

local VA medical center or military treatment facility. Veterans can be referred for further evaluation at specialized referral centers established by VA and DoD.

GW veterans and their eligible family members can register for medical examination and treatment by calling toll-free telephone numbers (VA: 1-800-749-8387; DoD: 1-800-796-9699). DoD has established a separate toll-free number (1-800-472-6719) for GW veterans to report details of incidents they believe may be associated with a medical problem experienced since returning from the Persian Gulf and for healthcare providers with questions about illnesses possibly related to service in the Gulf War.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5F: Psychological Health

Reference: ***Psychological Health of Gulf War-era Military***
Military Medicine. 1996 May;161(5):257-261.

Authors: LTC Robert H. Stretch, MSC USAR; CPT Paul D. Bliese, MSC USA;
David H. Marlowe, Ph.D.; Kathleen M. Wright Ph.D.;
LTC Kathryn H. Knudson, MSC USA; Charles H. Hoover, B.A.

Introduction

Although psychiatric casualties were low during Operations Desert Shield/Desert Storm, service members were exposed to the traumas of war either directly through combat operations or indirectly through exposure to the aftermath of combat. These service members represented potential mental health casualties. The purpose of this study was to assess the general physical, psychological, and psychosocial health and adjustment (including risk for development of post traumatic stress disorder [PTSD]) of veterans in Pennsylvania and Hawaii who either deployed or did not deploy to determine the need, if any, for additional resources by the Department of Veterans Affairs to resolve any potential readjustment problems resulting from service in Southwest Asia during the Gulf War.

Methods

The population samples consisted of over 16,000 active duty personnel assigned to units in Hawaii and Pennsylvania. From this population, the deployer sample consisted of 715 active duty veterans and 766 reserve veterans. The non-deployer sample consisted of 1,576 active duty and 948 reserve veterans. All participants anonymously completed a questionnaire that consisted of self-reported information on demographics, psychological and psychosocial health symptomatology, presence of symptoms specifically related to deployment and life in a combat theater, physical health symptomatology, perceived sources of past and current psychological stress (i.e., environmental demands exceeding the individual's ability to cope), perceived levels of current psychological stress, causal attributions of present problems, unit cohesion, social support, and the perceived impact of deployment.

Results

Those veterans who deployed to the Persian Gulf area were asked a series of questions about any stressors they may have experienced while deployed and how stressful they found each to be. The first set of stressors consisted of apprehension, anxiety, and, in a number of cases, exposure to possible traumatic events of combat. Directly experienced traumatic events were stressors for a large minority of deployed veterans. The most widely shared stressor for deployed veterans was the period of waiting for deployment. The major source of chronic stress within the combat theater were those related to conditions of life and work. A final source of stressors consisted of issues involving family and home.

The most widely cited problems for both deployers and non-deployers were financial matters, the way things are usually done in their ship/unit, career and chances for promotion, and personal future and the meaning of life. With few exceptions, these problems were of greater concern for deployers than non-deployers.

Data on psychological health were gathered with the Brief Symptom Inventory (BSI) which includes nine symptom dimensions or subscales. Both deployers and non-deployers differed markedly in comparison to civilian non-patient norm reference groups. Deployers scored significantly higher than "normal" as defined by the civilian non-patient norms. Although the non-deployer scores were in the high range, they were

not significantly different statistically from the civilian non-patient norms. In addition, the BSI mean scores for the active duty deployers were significantly higher than those of the non-deployers across all subscales.

The gross results suggested that deployers and non-deployers had modest, but real, differences in psychological outcomes as measured by the BSI. The findings, however, are tempered by the fact that the deployed and non-deployed groups tended to differ on a number of demographic variables that might explain the differences as well as, or better than, deployment.

Discussion

The results of this study demonstrated that those veterans who deployed to the Persian Gulf in support of Operations Desert Shield/Desert Storm experienced significant levels of stress. The results also demonstrated that stress remains a current daily fact of life for those who deployed. The data on general psychological health taken from respondents' BSI scores also demonstrated that caution must be used when interpreting these scores. Compared to civilian non-patients, the deployed veterans' scores were significantly higher on most subscales. Compared to other active duty and reserve soldiers who did not deploy to the Persian Gulf, the deployed veterans' BSI scores were essentially identical.

A problem with the comparison of BSI scores is that the "norms" for participants in a military subculture may not be the same as those for a civilian cohort. Thus, a "normal" military sample may not look the same as "normal" civilian non-patients. This could be the result of exposure to military-specific events (such as deployments, training experiences, etc.), the result of self-selection in that individuals with certain psychological traits may be drawn to the military, and the consequences of participation in the special subculture of the military.

Overall, findings from this study supported the conclusion that deployment did not result in any significant increases in psychological distress (as measured by the BSI) relative to other military personnel who did not deploy to the Persian Gulf. However, the deployers in the current study do remain significantly different from the non-deployers in terms of higher BSI scores, which was not the case with deployers contrasted to non-deployers in the authors' previous studies of post-Operation Desert Shield/Desert Storm Army veterans. This would indicate that, although the overall levels of psychological distress for those individuals in the current study (both deployers and non-deployers) may be lower than those of other samples previously studied, there are still differences within the present sample based on deployment.

Although there are differences between BSI scores of deployers and non-deployers, deployment status plays only a minor role in the ability to predict respondents' scores. With demographic differences and smoking/drinking behavior accounted for, deployers have BSI scores that are, at most, 4% higher than the scores of non-deployers. Although small, these differences cannot be dismissed as trivial. Even 4% may constitute a significant difference in the context of 400,000 personnel deployed to the Persian Gulf. It may well indicate that a subset of the population is experiencing significantly more psychological distress than its members would have if they had not deployed.

As the military continues to draw-down in response to the end of the Cold War, the likelihood of deployments into limited warfare and peacekeeping scenarios throughout the world increases. These deployments will present U.S. forces with ongoing and new stresses. Pre-deployment baseline assessments of units most likely to deploy should be made, otherwise attempts to try to explain the stress patterns and readjustment needs of returning veterans will continue to be made post hoc. To facilitate these assessments, a need exists for military-normed assessment instruments.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5F: Psychological Health

Reference: ***Psychological Symptoms and Psychiatric Diagnoses in Operation Desert Storm Troops Serving Graves Registration Duty***
Journal of Traumatic Stress. 1994 Apr;7(2):159-171.

Authors: Patricia B. Sutker, VAMC New Orleans; Madeline Uddo, VAMC New Orleans; Kevin Brailey, VAMC New Orleans; Albert N. Allain, VAMC New Orleans; Paul Errera, VAMC Washington D.C.

Background

Recent studies show that disaster rescue workers and military personnel assigned duties of recovering and identifying human remains have been traumatized by their experiences. The psychological effects of exposure to mass death have also been demonstrated in workers who were close to, but not necessarily directly involved with, recovery and identification. These studies point to traumatization among rescue workers assigned duties of recovering and identifying human remains in a disaster situation. The psychological impact of such duties among war zone troops has not been explored. In this report, the authors hypothesized that war zone troops exposed to human remains as part of their duty assignment, though not help-seeking or designated by patient status, would exhibit evidence of psychological distress, specifically negative mood states such as symptoms of depression, anxiety and anger, heightened concerns for bodily functioning, symptoms of post-traumatic stress disorder (PTSD) and, in some cases, sufficient psychopathology to warrant diagnostic labeling of clinical disorders, specifically PTSD.

Methods

Participants were 24 troops of a 35-member Army Reserve Quartermaster Company who were assigned graves registration duties and mobilized to military action in Saudi Arabia. A comprehensive psychological and psychiatric evaluation protocol was devised to assess variables thought to be pertinent to understanding war trauma events and their potential impact on psychological functioning and possible mental disorders. Respondents were also asked to complete a short questionnaire requesting personal demographic and history information.

The measurement scale for severity of war zone stress and its perceived critical elements reflected perception of injury and death, unpreparedness for deployment and combat, sense of unit cohesiveness, harshness of physical environment, perceived level of national support for the war, and stress attributable to nonmilitary events. Symptoms of psychological and physical discomfort were categorized as negative mood states such as anxiety, anger, and depression; somatic discomfort and physical concerns; and features considered specific to PTSD. Diagnosis of mental disorders were assigned when threshold criteria were met, and frequencies were determined for each disorder, including PTSD related specifically to participation in Operation Desert Storm.

Results

Content analysis of one of the instruments used in this study yielded four major themes of stress exposure: human casualties, suffering, and death; separation from home, family, and friends; loss of control, uncertainty and fear of the unknown; and austere physical environment and inadequate living conditions. Written replies in addition to statements made during clinical interviews showed that all of the sample troops were exposed to threat to life during war zone duty and to the gruesomeness of identifying and processing human remains.

Troops endorsed symptoms of negative mood states and psychological distress on measures of depression, anxiety, anger, and health discomfort.

Symptoms suggestive of trauma-related psychopathology, or symptoms of PTSD, were prevalent. The most common endorsements outlined were avoidance of thoughts or feelings associated with traumatic events, exaggerated startle response, recurrent intrusive recollections of traumatic events, loss of interest in usual activities, irritability, and anger outbursts. Also salient were avoidance of activities or situations arousing recollections of traumatic events, intense psychological stress upon exposure to trauma-related events, concentration difficulties, sleep disturbance, hypervigilance, and interpersonal distancing.

Data showed that one-half (12) of the troops met criteria for at least one current psychiatric diagnosis, whereas the other 12 soldiers did not evidence symptoms warranting current diagnosis. Forty-six percent of the sample were assigned current diagnoses of PTSD that was related to Operation Desert Storm. A high prevalence of comorbid psychopathology was associated with current PTSD diagnoses. Other prevalence rates were 25% for major depression, 17% for alcohol abuse/dependence, 8% for depressive disorder, and 4% for simple phobia. Review of the distributions of negative mood state and physical distress data suggested that there may be a bimodal clustering of extreme scores such that troops manifesting current PTSD, for example, endorsed depressive features and other negative symptoms in greater frequency and intensity than troops who were not labeled by PTSD.

Discussion

These descriptive findings suggested that symptoms of psychological distress and physical discomfort, as well as diagnosable psychopathology, may develop among individuals with no preexisting psychopathology subsequent to service in a war zone, particularly involving performance of duties that demand contact, recovery, and identification of human remains. The results revealed that half of the men and women reported symptoms and psychological discomfort sufficient for labeling by current psychiatric diagnosis. Forty-six percent of the troops were judged to suffer frank PTSD, and there was evidence of relatively high rates of disorder comorbidity, particularly associations between depressive and substance abuse disorders and PTSD. Many of the troops reported indications of psychological and physical distress, although these symptoms tended to be more frequent and more intense among troops assigned PTSD diagnoses. Roughly one-third admitted feeling nervous and fatigued and having problems with concentration, general aches and pains, and headaches. Data derived from this study demonstrated the need to explore more carefully the psychological and physical symptom constellations common among GW returnees and the relationships between psychiatric disorder, specifically PTSD, and exaggerated somatic concerns.

Exposure to death in the form of human remains represents a significant stressor and may well result in traumatization, even among psychologically robust persons. The prevalence of psychopathology judged to predate war zone deployment was minimal; it is reasonable to conclude that the psychological distress was derived from military duty and its aftermath. These and other findings underscore needs for adequate military preparation for graves registration assignment, skillful debriefing of war zone troops after combat service, and systematic follow-up to determine patterns of symptom expression and chronicity. In the case of at least one-half of the sample, and perhaps more, options for psychotherapeutic interventions must also be considered, particularly strategies for teaching positive coping mechanisms and aids to managing anger, depression, and anxiety, as well as symptoms of PTSD.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5F: Psychological Health

Reference: ***War Zone Stress, Personal Resources, and PTSD in Persian Gulf War Returnees***
Journal of Abnormal Psychology. 1995 Aug;104(3):44-452.

Authors: Patricia B. Sutker, VAMC New Orleans; J. Mark Davis, VAMC New Orleans and University of Georgia; Madeline Uddo, VAMC New Orleans and Tulane University School of Medicine; Shelly R. Ditta, VAMC New Orleans

Background

Research and clinical observations have indicated that a predictable pattern of psychological symptoms, labeled PTSD, may develop subsequent to the experience of extraordinary or life-threatening trauma, although not all outcomes to severe or life-threatening stress are negative and debilitating. In this study, the authors hypothesized that response to war zone stress, whether adaptive or marked by psychological distress, varies as a function of variables classified in personal and environmental resource domains, in addition to the potent impact of stress severity and trauma characteristics.

Methods

Participants were 775 troops deployed to combat in the Gulf War. Two troop subsets were identified for comparison: troops with self-reported PTSD symptoms sufficient to warrant disorder diagnosis (N = 97) and those reporting no evidence of PTSD or other psychological distress measured in this assessment (N = 484).

The authors conducted a series of stepwise discriminant-function analyses to study associations between personal and environmental resource variables and psychological outcomes subsequent to war zone stress. Within the category for personal characteristics and resources, the authors selected measures of personality hardiness, coping strategies, and intellectual sophistication. To reflect the environmental resources domain, the measures of social and family support and satisfaction were selected. Two measures of PTSD and two measures of psychological distress were used to identify and characterize the troop subsets compared in this study.

Results

As a group, GW troops showed minimal psychological distress on the instruments administered. Troop subsets identified for this study differed significantly on the personal and environmental resource variables explored. Univariate analyses of variance indicated that PTSD-diagnosed troops showed more avoidance, wishful thinking, and self-blame coping and less problem-focused coping strategies than those who reported no psychological distress, but the subsets did not differ in social support coping. PTSD-diagnosed troops produced lower scores on the hardiness dimensions of commitment, control, and challenge. Subsets did not differ in intellectual sophistication. Troops assigned PTSD diagnosis reported fewer and less satisfaction with social supports and less perceived family cohesion and expressiveness than their counterparts who had no psychological distress.

Results showed that among troops exposed to war zone stress, certain factors within the domains of personal and environmental resources were associated with stress-related symptoms, or conversely, with their absence following war participation. A combination of resource variables distinguished troops categorized as PTSD-disordered from those who lacked PTSD symptomatology. Prediction on the basis of four variables was relatively successful, yielding correct assignment in 87% of the overall sample.

Discussion

Among the factors of interest in this study, personal resource variables appeared to be more strongly related to psychological vulnerability or resistance to the negative impact of war zone duty

than were the resources selected from the environment domain. Personal resources accounted for 35% of the variance in discriminating troop subsets, whereas the remaining variables accounted for 5%. Although the commitment disposition of the hardiness construct appeared to function as a relatively strong resistance resource, there is also the possibility that lower scores on hardiness measures simply confirm the presence of PTSD as a disorder. Compared to personal resources and characteristics measured, demographic variables did not contribute as significantly to group prediction, even though troop subsets differed in ethnicity, education, and rank. The role of family and social support as agents to protect persons from the potentially pathogenic influence of stressful events was not as strongly related to mental health outcomes among GW troops as personal resource factors.

A combination of resource variables distinguished troops categorized as PTSD-disordered from those who lacked PTSD symptomatology. Personal resource variables appeared to be more strongly related to psychological vulnerability or resistance to the negative impact of war zone duty than were the resources selected from the environment domain. Commitment disposition of the hardiness construct appeared to function as a relatively strong resistance resource, although there is also the possibility that lower scores on hardiness measures simply confirm the presence of PTSD as a disorder. Results also revealed a significant association between PTSD symptoms and avoidance coping strategies, a finding of relationship that, as was acknowledged for hardiness results, did not convey information about direction of the causal pathway.

Results of this study are consistent with the notion of a diathesis-stress model of PTSD (i.e. stress alone is not sufficient to evoke psychopathology and some individuals are more inclined to mental health stability than others). Resource variables can be seen as possible moderators or conditions that qualify the relationship between stressor events and mental health outcomes. Because of acquired or inherited vulnerabilities or dispositions, some susceptible members of military units were perhaps at greater risk than others for developing PTSD when exposed to war zones. Conversely, certain variables can be hypothesized to moderate the relationship between stress and psychological outcomes. Following this logic, hardiness personality style and cohesive family relationships, as examples, may have existed prior to war zone duty and operated to protect the asymptomatic group from developing symptoms of PTSD and other psychopathology.

Without the use of a prospective design, it is impossible to determine whether resource factors existed differentially between groups prior to war stress exposure. As such, differences in personal and environmental resource factors after exposure to war stress may reflect disrupted personality dispositions and interpersonal relationships symptomatic of stress-related psychopathology. The present retrospective time frame permits only associative links between variables identified as effective in predicting war-related psycho-pathology. Use of a discriminant function model precludes testing possible causal pathways and the relative contributions and potentially mediating and moderating effects of variables on outcomes of interest.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5F: Psychological Health

Reference: ***Assessment of Psychological Distress in Persian Gulf Troops: Ethnicity and Gender Comparisons***
Journal of Personality Assessment. 1995;64(3):415-427.

Authors: Patricia B. Sutker, VAMC New Orleans; John Mark Davis, VAMC New Orleans; Madeline Uddo, VAMC New Orleans; Shelly R. Ditta, VAMC New Orleans

Background

Previous studies, particularly those involving comparisons of men and women, lack sufficient numbers of participants and suitable comparison samples to allow meaningful conclusions. Nevertheless, research has suggested that psychological disturbances, and PTSD specifically, may be greater among ethnic minority and women veterans of military service. This study used data collected by psychological assessment in a sample of troops mobilized by Operation Desert Storm. The hypothesis was that ethnic minority status and female gender are associated with higher levels of psychological distress, including negative mood states, complaints of physical discomfort, and PTSD symptoms, following war-zone duty.

Methods

Participants were 912 military personnel derived from 1,423 troops mobilized for active duty during the Gulf War who underwent psychological debriefing and evaluation within one year of war-zone return. They were divided into 653 war-zone-deployed and 259 stateside-duty military personnel. The sample reported an average age of 29 years and comprised white (63%), African-American (28%) Hispanic (8%), and other (Asian-American and Native American, 1%) troops. Percentages of women and officers were 14% and 9%, respectively.

Participants were administered a battery of paper-and-pencil psychological tests. Measures of psychological distress focused on current feelings and symptoms, reasoned to reflect post-war-zone functioning rather than more stable characteristics spanning a broader time frame, including prior to war-zone duty. PTSD symptoms were measured only among war-zone-deployed troops.

Results

Comparisons of troops deployed to the war zone and those assigned duty stateside on measures of psychological distress revealed significant differences on two measures of depression, an index of state anxiety, and somatic complaints. Twenty-two percent of war-zone-deployed troops reported at least mild levels of clinical depression. GW troops also scored higher on depression and anxiety scales and endorsed more somatic discomfort and physical complaints than personnel who remained stateside. Other frequently endorsed items, although not significantly different, included headaches, general aches and pains, and sleep problems.

Minority troops reported more depression than nonminority troops regardless of war-zone assignment, and more minority than white troops were classified as depressed. In addition, men and women differed in reports of physical symptoms, with women tending to endorse more physical and somatic complaints than men, regardless of war-zone assignment. Women more frequently admitted headaches, lack of energy, and upset stomach.

Comparisons of gender and ethnicity subsets on measure of PTSD among military troops who served in the Gulf War showed that ethnic minorities reported more symptoms than whites. The results also showed a tendency for minority, particularly male minority, troops to report more

psychological distress and PTSD symptoms, although the conclusion could not be made that minority troops, generally speaking, may have been more negatively impacted by Gulf War exposure. Further, minority troops tended to score higher on measures of depression than their non-minority counterparts, regardless of gender, and this tendency toward pessimism or dysphoria may account for the apparent increase in symptoms of PTSD. Female GW veterans did not report greater symptoms of psychological distress than their male counterparts or score higher on measures of PTSD symptomatology. Although women endorsed more symptoms of physical discomfort and somatic concerns regardless of war-zone duty, this tendency was not increased by war-zone exposure.

Discussion

The results of this study suggest that the experience of war-zone duty was associated with higher levels of post-military-duty psychological distress, specifically symptoms of depression, anxiety, and physical discomfort, than was found for troops who remained stateside, regardless of gender and ethnicity characteristics. These findings are noteworthy, because the study compared sizeable samples of demographically similar military troops who differed in war-zone exposure. The finding that 22% of troops deployed to the Gulf War reported at least mild levels of depression compared to 9% of those who served stateside within the first year of such military duty is of clinical significance. Comparisons with stateside troops were not available on measures of PTSD, but 12% of war-zone-deployed troops met criteria for PTSD diagnosis. Complaints regarding physical distress and somatic discomfort were higher among war-zone-deployed troops than those who remained stateside, regardless of ethnicity and gender. The one item that emerged as statistically significant was that of lack of energy, or fatigue, reported by war-zone troops in general.

Among the strengths of this study are assessment of psychological symptoms in sizeable samples of mobilized troops and recruitment from the community rather than from a treatment-seeking population. There are, however, limitations in study methods that suggest the need for caution in interpretation of present findings:

1. data were collected by self-report measures;
2. measures of PTSD symptoms were administered only among the war-zone-deployees subset; and
3. responses were collected during the first year subsequent to war-zone exposure.

Regardless of these study limitations and the need for replication, results point to the potentially negative psychological impact of war-zone exposure among troops generally and suggest that ethnic minorities may be more vulnerable to the risk of negative psychological sequelae. The possibility that women in military service may be at no greater risk of war-zone stress exposure sequelae than their male counterparts is interesting, given the increased numbers of women serving such duty. To what extend these findings may be extended for women as their role in direct combat and fighting is expanded has yet to be determined.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5F: Psychological Health

Reference: ***Reassessing War Stress: Exposure and the Persian Gulf War***
Journal of Social Issues. 1993;49(4):15-31.

Authors: Jessica Wolfe; Pamela J. Brown; John M. Kelley, VA Medical Center, Boston

Background

Despite the fact that the Gulf War was believed to have few adverse consequences for military personnel, anecdotal and clinical reports from soldiers suggested that exposure to a number of traditional and novel stressors occurred. Although empirical work has demonstrated adequate psychometric properties for a number of combat exposure scales, some important methodological issues still exist. For example:

1. as studies of PTSD evolve, more questions have arisen about the need for specificity of stressor characteristics to assess their interaction with subject-level characteristics;
2. presently used scales may not be descriptive of (or sensitive to) distinctive experiences of female, ethnically diverse, married, and older military personnel who represent rapidly growing segments of the volunteer-based U.S. Armed Forces; and
3. the time between self-reported stressor exposure and stressor onset may be confounded by the format and administration of scales.

Method

The authors conducted a series of statistical analyses to investigate the potential impact of certain variables on psychological adjustment, focusing particularly on the relationship of traditional exposure measures as compared to the relationship of newer scales developed or modified following the Vietnam War. Because follow-up phases of this longitudinal study are ongoing, the authors provided data from the acute evaluation phase, a period not typically explored in wartime studies. These data depicted some critical effects of wartime exposure on very early outcomes following military deployment. The authors had the following goals:

1. to review existing parameters in the traditional measurement of war-zone exposure;
2. to consider conceptual and methodological limitations in these approaches;
3. to present empirical data from a cohort of GW veterans that support the utility of a broader conceptualization of war trauma, and
4. to examine how gender may be differentially associated with some dimensions of war-zone stress and psychological outcome following deployment.

The Ft. Devens Operation Desert Storm (ODS) Reunion Survey was designed to investigate dimensions of war stressors and their effects following the conclusion of the Gulf War. The ODS Reunion Survey consists of a series of standardized measures and these were administered to veterans within five days of their return to this country before they rejoined their families, thus offering some of the earliest systematic data on soldiers' experiences during the conflict. Based on findings from existing exposure measures and feedback from veterans, the ODS Reunion Survey chose to investigate three major stressor categories: traditional wartime activities, non-traditional wartime events, and nonwar-zone, deployment-related experiences. All respondents provided information on these three stressors in three ways: a fixed format checklist ("traditional Laufer combat") involving minor modifications of previously validated combat exposure questions; a

fixed format checklist expanded to reflect ODS war-zone experiences ("ODS expanded checklist"); and an open-ended format where respondents described the single most distressing incident during their deployment period ("self-generated stressor categories").

Summary scores on the Laufer combat and ODS exposure scales were developed as the sum of the number of occurrences of all events. A more qualitative analysis of soldiers' exposure to combat and deployment (including domestic) stressors was conducted using subjects' self-generated descriptions of their single most stressful deployment event. To assess initial psychological outcome, measures of both PTSD and general psychological distress were included.

Results

Using the traditional (Laufer) combat scale and a five-level combat exposure classification scheme based on the Vietnam experience, 56% of men and 58% of women in this sample scored in the lower ranges for traditional combat activities. Only 3% of male and 3% of female returnees would be classified as having high levels of traditional combat exposure according to this scale. No significant differences were found between male and female veterans. The more comprehensive ODS expanded checklist yielded higher mean scores and showed that the three most commonly endorsed war-zone experiences for both genders were similar: formal alert for chemical or biological attack, receiving incoming fire from large arms, and witnessing death and/or disfigurement of enemy troops.

The distribution of self-generated stressor categories was significantly different for males and females. Combat stressors were the most widely selected and noncombat, war-zone stressors were second in prevalence. Primacy of domestic stressors were reported by approximately one-fourth of the men and women; only a small percentage reported no critical stressor. Although the prevalence of presumptive PTSD was relatively low, a substantial number of returnees reported high levels of general psychological distress. Examination of the behavioral checklist of stress-related symptoms showed that individual PTSD symptoms occurred at considerable rates and were significantly different for males and females.

Discussion

Results showed that Laufer combat and ODS expanded exposure scores did not differ significantly between men and women. Both scores were associated with psychological and PTSD outcome measures, a finding consistent with prior research employing traditional combat scales. Although the Laufer scale was a significant predictor of outcome measures, components of the expanded wartime measure were as significant. All ODS checklist factors were significantly related to outcome.

Considering the available background and combat exposure variables, PTSD symptoms (as defined by the PTSD checklist) were best predicted by regression models, although models predicting other outcome measures were significant as well. This finding may reflect the low rates of formal PTSD and other psychiatric disorders in the sample as well as our choice of outcome measures. Adjustment of women in the sample was significantly affected by certain back-ground and event-based characteristics. Prior wartime service also was predictive of outcome for women, but not for men. Age was also identified as a risk factor and had an inverse relationship to outcome. Other variables were not described.

Although the findings suggest that female personnel were more symptomatic in response to certain wartime stressors, at least during the initial postdeployment phase, these results should be interpreted cautiously. First, reporting style was not assessed and social desirability in reporting psychological states may differ considerably between men and women. Second, some potentially critical experiences, such as prior sexual or criminal victimization which may predispose to subsequent distress, were not evaluated. In addition, one possible decisive stressor--sexual harassment or assault during the

deployment--was not addressed in the initial survey phase. Thus, stressor assessment as it relates to gender-specific experiences should be pursued in greater detail.

This project offered an unusual opportunity to track the perceptions, experiences, and reactions of a relatively diverse group of deployed individuals after war. The data confirmed that a host of event, social environment, and personal characteristics should all be considered in the development of more valid models of post-trauma outcome. The current findings did not suggest that new exposure scales are needed for all subsequent military conflicts or catastrophic occurrences. Rather, the results pointed to the conceptual and clinical utility of evaluating stressors more precisely, in this case in light of the changing composition of wartime forces and military experiences. Overall, these data served two purposes: to alert clinicians and researchers alike to the importance of obtaining early baseline data and the importance of broadening identification and measurement of components of exposure as population demographics and types of trauma evolve over time.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5G: Toxicology

Reference: ***Acute Oral Toxicity Study of Pyridostigmine Bromide, Permethrin and DEET in the Laboratory Rat. Toxocological Study 75-48-2665***
Toxicological Study 75-48-2665. Prepared for the U.S. Army Medical Research and Materiel Command, Fort Detrick, Fredrick, Maryland by the Health Effects Research Program, Directorate of Laboratory Science, U.S. Army Center for Health Promotion and Prevention Medicine, 31 May 1995.

Principal Investigator: Wilfred C. McCain, Ph.D.

Background

This preliminary study examined the possible harmful effects of three compounds (pyridostigmine bromide, permethrin and DEET) when used individually and in combination. For this study, conducted in rats, the critical questions were:

1. what levels of use would be lethal to laboratory rats, and
2. whether or not the lethal effects would be higher when these three compounds were combined than would be expected by adding up the effects of the three compounds individually.

Definitions

1. Pyridostigmine bromide: an FDA-approved compound for the treatment of myasthenia gravis (a neurologic condition); used in the Gulf War against the possible effects of chemical weapons.
2. Permethrin: an EPA-approved insecticide used in many household and agricultural products; during the Gulf War, aerosol spray cans received only limited distribution within theater during the conflict.
3. DEET: an EPA-approved insect repellent that was used in the Gulf War.

Overview

This study investigated the lethal interaction of pyridostigmine bromide (PB), permethrin, and DEET when given to adult male rats by gavage. The study was separated into two phases. Phase I determined the acute oral lethal dose-response relationship of each compound with the vehicle, propylene glycol. Phase II was divided into two parts. The first part (positive control) was a dose-response study using probit units obtained from Phase I (LD 16, 30, 50, 70, and 84). Dosage solutions for the second (interaction) part of Phase II contained the calculated LD(16) (additive LD[32]) of two compounds while the concentration of the third compound was varied. Rats were fasted overnight, dosed, and observed for 14 days. A significant increase in lethality occurred when PB, permethrin, and DEET were given concurrently when compared to additive values. This information suggested that lethality in this study was more than an additive effect. Dosage levels of compounds used in this study were sufficient to produce lethality following a single dose and were far in excess of conceivable human exposure levels. For example, in order for an average 70 kg (155 lb) service member to become exposed to the lowest doses used in this study (PB = 46 mg/kg, Permethrin = 279 mg/kg, DEET = 1,946 mg/kg), this person would have to simultaneously ingest 107 PB tablets (30 mg each), 23 six-ounce cans of 0.5% permethrin

aerosol spray, and 6.6 two-ounce tubes of 33% DEET. Human exposure, however, would most likely occur at low levels over an extended period of time and by differing routes.

Discussion

As designed, the study demonstrated that a massive oral exposure of the three compounds killed laboratory rats. This can occur whether the compounds were administered individually or in various combinations. When all three were used together, the effects on laboratory rats were greater than the additive effect, but the combination of DEET and permethrin did not produce a greater than additive effect.

The results of this study indicated that a significant increase in lethality occurs when PB, permethrin, and DEET are given concurrently to male rats by gavage. Furthermore, solutions containing PB and permethrin or PB and DEET also caused a significant increase in lethality when compared to expected additive values. This information suggested that lethality in this study was more than an additive effect. The study also provided new information on the lethal effects of permethrin when used in conjunction with the vehicle, propylene glycol.

There are at least two possible mechanisms which, by concurrent oral exposure to compounds used in this study, could increase lethality. For instance, PB, which has a steep dose-response curve, is poorly absorbed by the gut. It is possible, therefore, that an increase in the bioavailability of PB could cause the increased lethality seen in this study. DEET, which has been used as a transdermal carrier molecule for the delivery of drugs and other agents, may enhance the uptake of PB from the gut. This would increase the levels of PB in circulation and decrease the activity of esterases. Another possible mechanism is the inhibition of detoxification systems. For instance, esterase inhibition by PB could also inhibit the degradation of permethrin, an ester. Hydrolysis of the ester bond in permethrin is mediated by non-specific esterases. Inhibition of this class of enzymes would effectively increase the residence time of permethrin in the body and may explain the increased lethality when these compounds are given simultaneously. Carbamates and pyrethroids are also degraded by cytochrome P-450 in the liver. This detoxification system may become overloaded with an increase in circulating levels of this toxicants. This would decrease the effectiveness of this enzyme system.

Conclusions

The study concluded that these substances may become more toxic when used in combination than when used separately. This study, however, was performed in rats that were given large doses of the three chemicals. Soldiers in the Persian Gulf were exposed to much smaller doses.

This study also used only one route of exposure in order to produce a quantifiable effect. The most likely human exposure scenario would be dermal exposure to permethrin and DEET and oral exposure to pyridostigmine. Mechanisms which caused increased lethality in this study may be partitioned if different routes of administration are used. Furthermore, dosage levels of compounds used in this study were sufficient to produce lethality following a single dose. As noted, human exposure would most likely occur at low levels over an extended period of time.

Another factor considered was the assumption of concurrent use. For instance, less than 5% of the deployed units had distributional access to permethrin for uniform impregnation. Furthermore, entomologists assigned in the Gulf during the conflict indicated a very low usage of personal repellents, including DEET, even at times and in areas where mosquitoes were present and biting. Also, the cool seasonal climate conditions which prevailed at the time of the war resulted in

the near absence of biting insects. In addition, PB was taken for about two weeks at the start of the air war and for a briefer period at the start of the ground war—a time when insect biting rates were extremely low. These factors indicate that the concurrent use of PB, permethrin, and DEET by service personnel was probably very low.

However, because several questions were not answered by this study, the suggestion was made that further research was indicated to determine whether these substances are among the causes of GW veterans' illness. Biopharmaceutic and pharmacokinetic studies would identify increases in blood levels of PB and decreases in esterase activity as well as alterations in clearance rates for compounds and metabolites.

Neuropharmacological, neuropathological and neurobehavioral assessment is also necessary in order to determine if nonlethal endpoints are neurological in nature. Another possible study could examine various routes of administration associated with the use of these compounds. The Department of Defense announced their intent to fund proposals from scientists across the country to address these questions.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

5G: Toxicology

Reference: ***Neurotoxicity Resulting from Coexposure to Pyridostigmine Bromide, DEET and Permethrin: Implications of Gulf War Chemical Exposures***
Journal of Toxicology and Environmental Health. 1996;48:35-56.

Authors: M.B. Abou-Donia, K.R. Wilmarth, K.F. Jensen, F.W. Oehme, T.L. Kurt

Background

During the Gulf War, service personnel were concurrently exposed to biological, chemical, and psychological environments. Potential exposure was to fumes and smoke from military operations, oil well fires, diesel exhaust, toxic paints, pesticides, fire sand, depleted uranium, chemoprophylactic agents, and multiple immunization. The reported chemical exposure included DEET and permethrin to protect against insect-born disease and pyridostigmine bromide (PB) to protect against possible nerve gas attack. Although these chemicals differ in many aspects such as chemical structure, use, mechanisms of action, and metabolic pathways, the major site of toxicity for all three is the nervous system.

Materials and Methods

This study investigated neurotoxicity produced in hens by individual or simultaneous exposure to these agents. The adult, leghorn, laying hens were considered specific-pathogen-free and medication-free without abnormalities of gait; they were vaccinated against common chicken diseases. The adult hen was chosen for the test animal because of its known susceptibility to anticholinesterase compounds and to allow direct comparison with ongoing studies of organophosphorus compounds in the laboratory.

Individual test compound studies were performed using the following dosages over the test period: PB, 5 mg/kg/d in water, po; DEET, 500 mg/kg/d, neat, sc; and permethrin, 500 mg/kg/d in corn oil, sc. A group of five hens was used as an untreated control group. Four groups of hens were given the following combinations: PB/DEET, PB/permethrin, DEET/permethrin, and PB/DEET/permethrin.

Spinal cord and sciatic nerve were excised immediately after sacrifice. Tissues were assessed with a step-down approach by first comparing sections from control and triple treatment groups, then double and single treatment groups were subsequently examined for any evidence of alterations observed in the triple treatment groups. Twenty-four hours following administration of the last dose, treated and control hens were anesthetized and decapitated; the brains were removed. Cholinesterase activities in plasma and brain homogenates were determined. Neurotoxicity was quantified by ranking control and treated hens according to severity scores.

Results

Animals treated with PB developed transient mild signs of cholinergic toxicity characterized by decreased activity and slight diarrhea. Animals treated with DEET developed rapid shallow breathing and tendency toward inactivity shortly after dosing, but recovered within 24 hours after dosing. Animals treated with permethrin did not exhibit any clinical signs. Only DEET-treated hens had significantly less weight at termination. All birds treated with single compounds survived the experiment. Neuropathological examinations of tissues revealed no difference between controls and PB-treated animals. Some animals treated with permethrin or DEET exhibited minor neuropathological changes.

Of the five animals treated with PB/permethrin, one developed a reluctance to walk and mild gait disturbance; another developed a fine body tremor. Animals treated with DEET/ permethrin or PB/DEET exhibited transient hyperexcitability between one and four weeks of dosing. In addition to clinical signs observed in animals treated with

the single compounds, animals treated with DEET/permethrin developed a transient leg weakness 9-14 days after the beginning of dosing. Animals treated with PB/DEET also exhibited intermittent diarrhea, marked shallow breathing, and decreased locomotor activity. Microscopic examination of spinal cord and sciatic nerve did not reveal any differences between control animals and those treated with PB/permethrin. Mild neuropathological alterations were observed in two of the animals treated with DEET/permethrin; middle to moderate alterations were observed in all animals treated with PB/DEET.

Concurrent treatment with PB/DEET/ permethrin caused severe diarrhea, shallow rapid breathing, and moderate inactivity within 15 minutes of dosing starting on the first day. At termination, hens from this group significantly lost weight. All animals developed a gait disturbance and exhibited body tremors after dosing. Animals treated with the three compounds exhibited neuropathological changes that ranged from mild to severe. A total of four of the five treated hens did not survive the experimental period.

In this study, the mean rank value was used to quantify and compare the neurotoxic effects of various treatments. The mean rank value for the control group was significantly less than the values for all treated groups except for hens treated with permethrin alone. Hens treated with two compounds (PB/DEET, PB/permethrin, or DEET/permethrin) had mean rank values significantly higher than for single treatments except for PB/permethrin which was not significantly different from DEET alone. Treatments with the three compounds had a mean rank value that was significantly higher than single- and two-compound treatments.

Clinical signs that developed shortly after dosing with test compounds were:

1. reluctance to walk and decreased activity in cage;
2. diarrhea; and/or
3. shortness of breath.

Persistent signs of neurotoxicity were categorized into two classes: locomotor dysfunctions and whole-body tremor. The results demonstrated that PB significantly increased the neurotoxic effect when combined with individual chemicals. For comparison of the permethrin/ DEET/PB group with the permethrin/ DEET group, the difference in the mean ranks was significantly higher in the permethrin/DEET/PB group. For the PB/DEET versus DEET comparison, the mean rank was significantly higher with PB/DEET; this appeared to be associated with an increase in locomotor dysfunction and changes in the spinal cord. Mean rank for PB/permethrin was also significantly greater than that for permethrin. The combined results also show the significant increase in neurotoxicity of the triple-compound treatment over the individual and binary treatments.

Discussion

This study demonstrated that concurrent administration of any two compounds of PB, DEET, and permethrin results in neurotoxicity that is markedly greater than that resulting from treatment with any individual compound. Additionally, neurotoxicity is further enhanced following concurrent administration of all three agents. Because combined treatments increased neurological deficits characterized by both peripheral nervous system and central nervous system injury, one might assume that this neurotoxicity resulted primarily from the direct action of DEET and permethrin, with PB playing an indirect role as it does not cross the blood-brain barrier. Inhibition of plasma BuChE enzymatic activity is consistent with the mode of action of the test compounds.

The authors hypothesized that competition for liver and plasma esterases by these compounds led to their decreased breakdown and increased transport of the parent compound to nervous tissues. Thus, carbamylation of peripheral esterases by PB reduced the hydrolysis of DEET and permethrin and increased their availability to the nervous system. In effect, PB "pumped" more

DEET and permethrin into the central nervous system. Consistent with this hypothesis, hens exposed to the combination of the three agents exhibited neuropathological lesions with several characteristics similar to those previously reported in studies of near-lethal doses of DEET and permethrin. If this hypothesis is correct, then blood and liver esterases played an important "buffering" role in protecting against neurotoxicity in the population at large. It also suggested that individuals with low plasma esterase activity may be predisposed to neurologic deficits produced by exposure to certain chemical mixtures.

The variety of symptoms reported by veterans make it unlikely that a single etiologic cause was responsible for Gulf War illnesses. Although this study was not intended to simulate actual exposure conditions that may have existed during the Gulf War (nor designed as a dose-response study), an hypothesis can be formulated as to why coexposure to test compounds may have contributed to GW veterans' illnesses.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

Chapter Six: Chemical Warfare Agents

Introduction

Veterans began reporting suspected exposures to chemical warfare agents shortly after returning from Operations Desert Storm and Desert Shield. VA carefully listened to veterans who expressed concern about exposure to chemical warfare agents in the Gulf War. VA's public statements have always made clear that all exposures, including neurotoxic exposures to low level chemical warfare agents, were being investigated. In 1995, VA began including questions about possible exposure to chemical warfare agents as part of the revised Registry examination exposure questionnaires.

In 1996, VA learned that GW participants who were involved in the demolition of an Iraqi ammunition storage facility known as Khamisiyah in southern Iraq in March 1991, may have been exposed to the nerve agents sarin and cyclosarin. In July 1997, DoD reported that a CIA computer model revealed that although no U.S. personnel experienced noticeable health effects from the release of these chemical agents, about 98,900 U.S. troops may have been exposed to very low levels of the agents.

Unfortunately, there is no valid biomarker to identify chemical warfare agent exposure that occurred years ago. Although computer models estimate the number of GW veterans and level of nerve agent exposure at Khamisiyah, no objective measurement of exposure exists. Research is continuing, and has been expanded in recent months, on the possible toxicity of low level chemical warfare exposures.

While long-term health effects due to very low-level (asymptomatic) exposures to organophosphate nerve agents are felt to be unlikely, GW veterans with health problems which they believe may possibly be related to chemical exposures are provided needed care, without charge to them, at VA medical centers across the Nation.

The Armed Forces Epidemiology Board reviewed the existing literature on the potential health consequences of exposure to low level chemical warfare agents. The summary analysis follows.

Reference: ***Long-term Health Effects Associated with Subclinical Exposures to GB and Mustard*** Environment Committee, Armed Forces Epidemiological Board, 18 July 1996.

Authors: Dennis M. Perotta, PhD, CIC, Chair, Environment Committee, AFEB

Background

Recent evidence by the Department of Defense Persian Gulf Investigation Team suggested that one bunker in Kamisiyah Ammunition Storage Depot in South Iraq may have held chemical weapons. U.S. soldiers from the 37th Engineer Battalion destroyed bunkers at this site in early March of 1991. Despite the complete lack of confirmatory evidence, this information highlighted the possible, though unsupported, concern regarding exposure to U.S. troops to chemical agents during Desert Storm. As a result, the Armed Forces Epidemiological Board (AFEB) was asked to conduct a literature review and to critique and comment on the following question: Are there observable long-term effects associated with exposure to Sarin (GB) and mustard at concentrations below that needed to cause acute signs, symptoms, or injury?

Findings

Most of this report provides information about Sarin (GB) and mustard (HD) based on a literature review and discussions with outside consultants knowledgeable in chemical weapons and/or toxicology. A summary of the findings follows:

Sarin (GB): Evidence indicates that GB does not have carcinogenic, mutagenic or teratogenic properties. Therefore, no increases in birth defects or cancer would be expected from low dose, subclinical exposure to GB. Follow-up of a cohort of men exposed to GB found no increase in hospitalizations, reported health problems, mortality, or other measured end points.

Some information in humans and animals suggested that repeated low-dose exposures to GB could result in subtle, but measurable (based on spectral analysis) changes in the EEG of exposed animals and men. It was unclear whether the doses used resulted in "no" or "few" minor symptoms in animals, but the men reported minor effects consistent with GB exposure. The type of EEG changes were similar in the two groups; an increase in the relative amount of beta voltage was found up to one year post-exposure in animals. The exposed group of men had significantly more beta voltage, relative to other voltage classes, than those who were not exposed to GB. The exposures were unintentional and occurred up to six years prior to the evaluation.

Neither the animal nor human studies regarding EEG changes directly addressed the exact question. The similarity in findings between human and animal studies suggested that this may be a true effect. Whether the effect occurs in humans exposed to levels lower than that needed to cause acute signs or symptoms was unclear. Also uncertain was the clinical significance of this finding, if real, to the soldier. This area deserves continued study, but the data are simply insufficient to recommend any additional action at this time.

Mustard (HD): This vesicating agent is well known to have carcinogenic potential, as it is a strong alkylating agent of DNA and RNA. This agent causes a variety of genetic lesions in many types of mammalian cells in a dose-response fashion. There is clear epidemiologic and toxicologic evidence that exposures to mustard (high enough to cause acute symptoms either on the battlefield or in test chambers) are associated with an increased risk of respiratory and skin cancers and perhaps leukemia. This estimate is of unknown precision since exact exposure information is not available.

The risk of cancer related to mustard at dosages less than that necessary to cause any acute effects is much less clear. Carcinogenesis is a dose-response phenomenon and very low exposures would have a very low risk associated with it. Additionally, the number of individuals exposed in any scenario of the Persian Gulf would be relatively few, making it unlikely that a

measurable increase in cancers could be detected. Finally, the length of exposure in these scenarios was extremely limited as compared to the standard decades of daily exposures that are used in carcinogenic risk assessment.

Using standard cancer risk assessment methodology, an estimate for cancer risk was calculated. In 1991, the U.S. Environmental Protection Agency derived a unit risk of 8.5 x10 (to the negative power of 2) per microgram/m3 for mustard. Considering a single 5 minute exposure to HD at a concentration of 0.05 mg/m3 (chosen to approximate a level 10% of a dose that might cause minimal signs and symptoms), the cancer risk was estimated as 5.8x10(to the negative power of 7). This essentially means that for every 10 million persons exposed under these circumstances, 6 additional cancer cases would be expected to arise from this exposure. Since no Desert Storm scenario included more that a few hundred to few thousand men at any one time, there would be no detectable additional cancer cases arising from this hypothetical scenario. It must be understood that changes in any of the assumptions of exposure will impact the final estimate and that this estimate was calculated with the understanding that no substantial evidence in support of exposure to HD during Desert Storm was found.

While animal experiments indicate that mustard is a reproductive toxin at high doses, there is little human information available to evaluate this risk in humans at high or low dose exposures. The scarce amount of information located for this review suggested that HD was not teratogenic.

There is ample evidence to suggest that severe exposure of skin to HD is related to a variety of long-term skin ailments such as pigmentary disorders, skin ulcers, and cutaneous cancers. There is insufficient information to judge if exposures lower than that necessary to produce an acute effect will have a long-term adverse health result.

There is evidence that severe exposure of the eye to HD, with concomitant acute injury, is related to adverse long-term ocular conditions. No evidence of such an effect was found for exposures lower than that necessary to cause an acute injury. The data were very limited in this area and insufficient for definite conclusions.

Exposure to high levels of HD causes significant damage to respiratory tissue and results in a variety of non-cancer respiratory conditions. There is no evidence that suggests short-term exposure to very low levels (less than necessary to cause any symptoms) of mustard is related to long-term health problems of the respiratory system. The data are very limited and the theoretical possibility of long-term effects without acute injury can not be eliminated totally.

Immune function can be depressed or altered as a result of high dose exposure to HD. No convincing evidence was found that such alterations occur over the long-term as a result of exposure to concentrations less than that which causes acute signs or symptoms.

While a thorough literature search was not conducted on psychological aspects of chemical agent exposure, one reference had potential use for addressing the question. Psychological dysfunction was related to the circumstances surrounding exposures to mustard in test chambers and field trials. These circumstances may parallel those experienced by soldiers in selected areas of Desert Storm; however, no conclusion is reached in this report.

Conclusions

No scientific data was located that directly applied to the question at hand and little that directly addressed the fundamental question. All the human studies found and reviewed dealt with persons exposed (intentionally or unintentionally) who reported signs, symptoms, or frank injury. In most of the reviewed studies, the definition of "exposed" was the presence of clinical effects of any degree.

Although the AFEB found several health effects for the two chemical agents that were related to high level exposure, there was no useful methodology found that could be used to

adequately extrapolate to the very low concentrations proposed in the question. The exceptions to that observation were those studies that were adequate to judge no effect at high doses. The results of the review showed that the long-term effects of limited exposures to sub-clinical doses of GB and HD are unclear, but the data suggested that health effects would not be detectable.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

Chapter Seven: Some Hypotheses Regarding Illnesses in Gulf War Veterans

Introduction

U.S. service members potentially were exposed to a wide range of risk factors during the Gulf War. A number of individuals and groups have proposed theories regarding the health consequences of such exposures to veterans. Independent oversight groups including the Presidential Advisory Committee on Gulf War Veterans' Illnesses, The National Academy of Science's Institute of Medicine (IOM) and the National Institute of Health Technology Assessment Workshop have performed comprehensive reviews of these issues. From their analysis of the information available to them, they have determined that these theories do not meet rigorous the scientific standards necessary to support an association with GW veterans' illnesses.

GW veterans are interested in the proposed theories and frequently ask healthcare providers to explain how the exposures are relevant to their present and future health. Therefore, it is important that healthcare providers be aware of these theories and can provide informed counseling to GW veterans regarding their concerns. In response to Public Law 102-585, the Institute of Medicine of the National Academy of Science appointed a committee to review the "Health Consequences of Service During the Gulf War" The committee completed its review and published a report in September 1996. Its report is the most comprehensive published report on the hypotheses about causes of the unexplained GW illnesses. The information provided in this chapter is a summary of the IOM's review of alternative hypotheses for GW veterans illnesses.

Reference: ***Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems***.
Washington, DC: National Academy Press, 1996:117-127.

Author: U.S. Institute of Medicine. Committee to Review the Health Consequences of Service During the Persian Gulf War

Background

In Chapter Five, many of the hypotheses encountered by the committee as it attempted to comprehensively investigate the health-related consequences of service in the Gulf War area are discussed. The hypotheses suggested a wide variety of associations among agents and exposures, circumstances that existed in the Gulf, and adverse clinical outcomes. These hypotheses had various degrees of plausibility and supporting research. The investigations and putative causal associations evaluated by the Committee demonstrated the vexing nature of the medical problem referred to by some as a "Gulf War Syndrome" and by the Committee as "unexplained illnesses."

Hypotheses

Hypotheses with supporting evidence presented to the Committee as a cause for veterans' unexplained illnesses are provided in this chapter. These include:

1. Chronic fatigue syndrome (CFS). This syndrome is of unknown etiology, occurs worldwide, and results in significant disability for the patient. There is a growing consensus that CFS may be a valid diagnosis. The classification of CFS is made when the criteria for severity of fatigue, the main CFS symptom, are met and four or more of eight symptoms are concurrently present or recurring for six or more months of illness not predating fatigue.
2. Multiple chemical sensitivity (MCS). Gulf War veterans who are experiencing multiple symptoms had their disease "induced" by one or more exposures in the Gulf. These include pesticides, solvents, drugs, or virtually any of the other agents encountered there; "triggering" of disease occurs after low-level exposures to similar noxious substances, likely becoming manifest after the return home of the affected troops. Four major views about the etiology of MCS are provided.
3. Oxidative phosphorylation disorder. Unexplained illnesses are caused by a disorder of the mitochondrial metabolism leading to encephalomyelopathy and is presumed to be linked etiologically with poor nutrition combined with increased metabolic demand.
4. Dental amalgams. Unexplained symptoms may be related to mercury toxicity occurring as a result of the installation of dental amalgams just prior to, or immediately after, service which results in clinically evident elemental mercury toxicity that continues as patients have ongoing exposure to mercury.
5. Bacterial illness. Persistent streptococcal or other bacteremia have been suggested as a cause of unexplained illnesses; the suspected bacteremia is proposed to resemble that encountered after dental procedures and is claimed to be diagnosable by using unique microscopic evaluation of the urine which streptococci enter from the blood via the kidney.
6. Mycoplasma and chronic fatigue. A subset of soldiers with unexplained illness of a type considered similar to CFS have mycoplasma infections that can be diagnosed if appropriate laboratory tests are available; no source of mycoplasma infection has been documented although mention has been made of the potential immunosuppressive effects of inhaled fine sand particulates present in the Gulf region.

7. Skeletal muscle bioenergetics. May share some similarity with disorders of oxidative phosphorylation; the investigative findings were suggested to potentially contribute to understanding the pathophysiology of fatigue; no cause for this fatigue was suggested.
8. Sarcoidosis and lingual abnormalities. The etiology of sarcoidosis is unknown and further research might be indicated, particularly since there has been some suggestion that sarcoidosis is exposure related. Some veterans were noted to have multiple linear inflamed areas along the cheek and occasionally along the dorsolateral surface of the tongue. These initial signs suggest that the patient is suffering multisystem effects of toxic exposures.
9. Brainstem dysregulation syndrome. This hypothesis suggests that two "insults" to the brainstem--one early in life and one later (e.g. while in the Gulf region)--could produce a polysymptomatic illness.
10. Microsporidia infection. Stool of GW veterans was examined to search for protozoal infections and the investigator suggested that microsporidia infection might be related to service in the Gulf War; an intensive follow-up examination of these findings identified no microsporidia.
11. Organophosphate-induced delayed neurotoxicity. Unpublished reports of the results of a study indicate that there may be some evidence of delayed neurotoxicity associated with symptoms in veterans; the report was been peer-reviewed, however, and the study has significant problems.
12. Chemically induced porphyria. This hypothesis indicates a concern that pesticide exposures in the Gulf region may have caused unexplained symptoms. These findings are similar to those for individuals who are reported to have MCS syndrome.
13. Fibromyalgia. Diagnosis is based on symptoms presented by the patient and one symptom-related physical finding: namely, at any of multiple sites of the body, pinching or pressure by a probing finger induces unexpected withdrawal or exclamations of pain. Patients often have symptoms that overlap those described for MCS and CFS. No definite exposure or experience has yet been linked to this entity.
14. Somatization disorder. An essential feature of this disorder is a pattern of recurring multiple somatic complaints that cannot be fully explained by any known general condition or by the result of exposure to any known substance. Physical complaints are in excess of those expected from evaluation of the patient. Individuals usually describe their complaints in colorful, exaggerated terms, but factual information is often lacking.

Conclusions

The committee reached several conclusions based on these descriptions of ongoing work.

1. Their diverse nature provided additional compelling evidence that no one disease entity will likely be adequate to resolve the understanding of all unexplained illnesses in Gulf War veterans.
2. These ideas, hypotheses, and investigations served as testimony to the efforts of many health professionals who strive to find avenues, overlooked by others, that might lead to new understandings of these illnesses and result in amelioration of the suffering that has occurred and continues to be reported.
3. Although these approaches have varying merit and the investigators are dedicated to solving the problem, the Committee was not optimistic that they are sufficiently well-substantiated to

offer much hope of important answers or relief for significant numbers of ailing American veterans.

4. Although the Committee has not identified an explanation for the unexplained illnesses in Persian Gulf veterans, it does not doubt that many individuals who report such illnesses are seriously affected.

Note: ***A copy of this article is available in Library Service at VA medical centers. Please ask for "A Guide to Gulf War Veterans' Health: 1997 Continuing Medical Education Program."***

Supplemental Reading

Coordinating Federal Efforts on Persian Gulf War Veterans.
Federal Practitioner 1995 December; 9-15

Peter Beach, Ph.D.; MG Ronald R. Blanck, D.O., MC, USA; Timothy Gerrity, Ph.D.; CAPT Kenneth Craig Hyams, M.D., M.P.H., MC, USN; Susan Mather, M.D., M.P.H.; John F. Mazzuchi, Ph.D.; Frances Murphy, M.D., M.P.H.; Robert Roswell, M.D.; and Raymond L. Sphar, M.D., M.P.H.

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A precedent among governmental agencies has been established that should continue after Persian Gulf health issues are resolved.

During Operations Desert Shield and Desert Storm, the United States deployed 697,000 military personnel to the Persian Gulf. Although morbidity and mortality rates were much lower than in previous wars, some veterans of the Gulf War have developed unexplained illnesses since returning home in 1991.[1–3] Both VA and DoD have developed comprehensive clinical evaluation and treatment programs to care for Persian Gulf veterans (Table 1).[3,4] HHS has not been responsible for the health care of Persian Gulf veterans but has been involved, along with VA and DoD, in extensive research efforts to study the nature and etiology of their illnesses (Table II).5,6 Consequently, all three departments—VA, DoD, and HHS—have developed complementary programs to deal with Persian Gulf veterans' health issues.

Because of the need to provide additional coordination for these related government activities, the Persian Gulf Veterans Coordinating Board was established on January 21, 1994. The Secretaries of VA, DoD, and HHS head the Coordinating Board, which was established under authority of Title 31 of the United States Code, Section 1535.

Table I. VA and DoD evaluation and treatment programs.

VA programs*

- Persian Gulf Registry Health Examination Program
- Specialized referral centers for complex and difficult-to-diagnose patients

  Washington VAMC, DC
  Houston VAMC, TX
  West Los Angeles VAMC, CA
  Birmingham VAMC, AL
- Special medical programs

  Depleted Uranium Surveillance Program at Baltimore VAMC, MD
  Neurocognitive Pilot Clinical Program at Birmingham VAMC, AL

DoD programs*

- Comprehensive Clinical Evaluation Program
- Specialized care centers

  Walter Reed Army Medical Center, Washington, DC
  Wilford Hall Medical Center, San Antonio, TX

*Veteran information concerning VA and DoD clinical programs is provided by two hotline numbers: for VA call 1-800-PGW-VETS and for DoD call 1-800-796-9699. Persian Gulf veterans with health concerns possibly related to the Persian Gulf War are encouraged to call on of these hotline numbers.

Mission

The mission of the Coordinating Board is to provide direction and coordination on health issues related to the Persian Gulf War within the executive branch of the federal government. Establishment of a secretary-level board to provide interdepartmental coordination is unique but was considered necessary to ensure that the three departments share a common understanding of the issues, to effectively allocate all available resources, and to provide a means of disseminating information.

The Coordinating Board has established three primary mission objectives:

- To provide all veterans the complete range of health care services necessary for medical problems that may be related to deployment in Operations Desert Shield and Desert Storm. This objective was aided substantially by passage of Public Law 103-210, which provides priority care at VAMCs for health problems possibly related to exposures during Persian Gulf service.
- To develop a research program that will result in the most accurate and complete understanding of the types of health problems being experienced by Persian Gulf veterans and the factors that have contributed to these problems.
- To develop clear and consistent guidelines for the evaluation and compensation of disabilities related to Persian Gulf service.

Organization

The three Secretaries who head the Persian Gulf Veterans Coordinating Board are assisted by a permanent staff and three working groups. The staff includes five health specialists: an executive director, two health administrators provided by VA, and two officers provided by DoD. The staff has dedicated office space in Washington, DC; administrative and clerical support is shared responsibility among the three involved departments.

The staff assists in all functions of the Coordinating Board, including daily operations of the Board, implementation of recommendations by the working groups, and rapid dissemination of relevant information. The primary liaison between Coordinating Board staff and the three departments is provided by: VA's Office of Public Health and Environmental Hazards, Washington, DC; DoD's Office of Health Affairs–Clinical Services, the Pentagon; and HHS's Office of Veterans Affairs and Military Liaison, Washington, DC.

The three working groups established by the Coordinating Board address specific issues related to medical care, research, and compensation and then provide recommendations to the three secretaries who comprise the Coordinating Board. Working group membership is drawn from administrative, clinical, and research specialists in VA, DoD, and HHS. The chair of each working group was selected by the three secretaries heading the Coordinating Board, and working groups meet at the discretion of the chairs (usually monthly, but

Table II. Major research efforts in VA, DoD, and HHS.

Epidemiologic research*

- VA's national, randomized mail/telephone survey of 15,000 Gulf War and 15,000 non-deployed Gulf-era veterans
- DoD's survey of Seabees and evaluation of active-duty hospitalization records
- HHS's survey of military personnel from Iowa
- CDC's case-control study of Pennsylvania National Guard/reserve personnel

Environmental hazards research

- Establishment of three research centers at VAMCs:
  - East Orange VAMC, NJ
  - Boston VAMC, MA
  - Portland VAMC, OR
- DoD research at Wright Patterson Air Force Base, Dayton, OH

Other research efforts

- The health effects of depleted uranium
- Possible synergistic effects of chemicals found in the Persian Gulf
- Development of improved diagnostic tests for leishmania infection
- The psychological consequences of Gulf War-related stress

*The epidemiologic research conducted is focused on determining the prevalence and potential risk factors of illnesses and adverse birth outcomes

more frequently when necessary). the specific functions of the three working groups are described below.

Clinical working group

The clinical working group provides direction and coordination for clinical efforts on behalf of Persian Gulf veterans. Oversight functions include coordination of VA and DoD Persian Gulf health registries and provision of comparable clinical assessment questionnaires and comparable laboratory examination protocols (Table I).[4,7]

The clinical working group ensures that the two clinical registries are clearly defined as a means for identifying and reporting illnesses among Persian Gulf War veterans. the group also develops educational tools and programs, publishes medical articles that assist clinicians caring for Persian Gulf veterans, and helps educate patients and the public about relevant health issues.[3]

Research working group

This working group provides guidance and coordination for VA, DoD, and HHS research activities related to the Persian Gulf deployment (Table II). Because of the President's designation of VA as the lead agency for research efforts in this area, VA's chief for research and development chairs this working group. A representative of the EPA also serves on this working group to advise on toxicologic issues possibly related to Persian Gulf service.

The research working group coordinates all studies conducted or sponsored by VA, DoD, and HHS to prevent unnecessary duplication and to ensure that resources are directed toward high-priority research questions. Specifically, this working group assesses the state and direction of research, reviews government research concepts as they are developed, identifies gaps in factual knowledge and conceptual understanding, recommends research directions, and collects and disseminates peer-reviewed research information.

Along with monitoring relevant new data and making it accessible, the research working group generates periodic reports to federal oversight authorities.[6] In addition, the research working group coordinates the development of a Persian Gulf research plan. This plan is one aspect of a dynamic assessment process that is reviewed at least yearly by the Coordinating Board. As part of this process, the research working group analyzes suggestions of review/oversight committees and makes recommendations to the Secretaries concerning appropriate research goals.[8–10]

The research working group serves as a forum for research data exchange among the three departments. A database of VA, DoD, and HHS research activities and accomplishments has been established in the VA Office of Research and Development, Washington, DC, to assist in information exchange, the generation of reports, and updating the research plan. The research database also includes copies of Persian Gulf research publications and abstracts that have resulted from government-funded studies. VA, DoD, and HHS share in the responsibility for tracking research projects and updating the research database.

Disabilities and compensation working group

This working group is responsible for assisting in the establishment of fair, clear, and consistent

guidelines for VA and DoD disability determinations and for compensation. Working group coordination was particularly important after December 8, 1994, when VA published new rules to provide compensation for certain disabilities due to undiagnosed illnesses among Persian Gulf veterans (pursuant to Public Law 103-446, known as "The Persian Gulf War Veterans Benefits Act").

Accomplishments

Although the Persian Gulf Veterans Coordinating Board is a novel concept that has been in operation only for a short period of time, it has been able to accomplish several objectives that have aided Persian Gulf veterans. One of the specific accomplishments of the Coordinating Board has been to ensure that the clinical evaluations conducted by VA and DoD are comparable and will generate complementary data. Accomplishment of this objective has required numerous meetings and much hard work due to the differences in patient populations, the differences in eligibility for medical care, and the difficulties inherent in providing uniform clinical assessments in numerous medical facilities, which are scattered in every state and in foreign countries.

Another accomplishment of the Coordinating Board has been to provide guidance to governmental researchers who are evaluating morbidity, mortality, and risk factors of disease among Persian Gulf veterans. This coordination will ensure that the major epidemiologic studies and investigations of potential environmental hazards avoid unnecessary duplication and provide comparable data. Additionally, new research findings are being rapidly disseminated among researchers via the centralized research database maintained by VA, DoD, and HHS. Furthermore, because of continuous oversight by the research working group, new and promising research directions are being identified.

In addition to these specific accomplishments, the Coordinating Board has been responsible for rapidly disseminating relevant clinical and research information on potential health risks, research findings, and health outcomes. Also, the Board has helped VA, DoD, and HHS coordinate preparations for Congressional briefings and hearings; the development of administration legislative proposals and positions; and more comprehensive responses to inquiries from Congress , review bodies, and the public. Importantly, the Coordinating Board has provided a forum for the exchange of ideas within the government and for the development of interdepartmental relationships, which have fostered treater understanding and cooperation.

Conclusion

The Persian Gulf Veterans Coordinating Board has been an effective mechanism for bringing together three separate government departments to work toward a common goal of serving the needs of Persian Gulf veterans. Because the Coordinating Board's mission is to assist three government departments rather than to supplant responsible agencies and programs, its work is not well known outside of VA, DoD, and HHS. Nevertheless, the Coordinating Board has been able to accomplish much for Persian Gulf veterans by helping ensure uniform clinical evaluations, appropriate health care, relevant research activities, specific and uniform guidelines for disability/compensation determinations, and cooperation withing the government. The Persian Gulf Veterans Coordinating Board has established a precedent of cooperation and effective government that should continue even after current Persian Gulf health issues are resolved. For VA and DoD—who share responsibility for the health care of a common patient population—future coordination is vital to answering questions related to health risks, medical records, and compensation.

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Authors

Peter Beach, PhD, is director of the Office of Veterans Affairs and Military Liaison, Immediate Office of the Secretary at the Department of Health and Human Services, Washington, DC.

MG Ronald R. Blanck, DO, MC, USA, is the commanding officer of the Walter Reed Army Medical Center, Washington, DC.

Timothy Gerrity, PhD, is deputy director of Medical Research Services at the Department of Veterans Affairs, Washington, DC.

CAPT Kenneth Craig Hyams, MD, MPH, MC, USN, is medical director of the Persian Gulf Veterans Coordinating Board, Washington, DC.

Susan Mather, MD, MPH, is assistant chief medical director of Public Health and Environmental Hazards at the Department of Veterans Affairs, Washington, DC.

John F. Mazzuchi, PhD, is deputy assistant secretary of defense, Health Affairs-Clinical Services at the Department of Defense, the Pentagon, Arlington, VA.

Frances Murphy, MD, MPH, is director of Environmental Agents Service at the Department of Veterans Affairs, Washington, DC.

Robert Roswell, MD, is executive director of the Persian Gulf Veterans Coordinating Board, Washington, DC.

Raymond L. Sphar, MD, MPH, is acting chief of Research and Development at the Department of Veterans Affairs, Washington, DC.

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